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(54) Title: SUBSTITUTED INDOLES, PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH INDOLES AND THEIR USE AS PPAR-γ BINDING AGENTS

(57) Abstract: Disclosed are substituted indoles, pharmaceutical compositions containing such indoles, and their use in treating or preventing PPAR-γ mediated diseases or conditions, such as osteopenia, osteoporosis, cancer, diabetes and atherosclerosis.

SUBSTITUTED INDOLES, PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH INDOLES AND THEIR USE AS PPAR-γ BINDING AGENTS

Field of the Invention

The invention relates to substituted indoles, pharmaceutical compositions containing such indoles, and their use in treating or preventing diseases or conditions mediated by the Peroxisome Proliferator Activated Receptor-γ (PPAR-γ).

Background

Peroxisome Proliferator Activated Receptors (PPARs) belong to the steroid/retinoid receptor superfamily of ligand-activated transcription factors. Willson, *et al.*, Curr. Opin. Chem. Biol., (1997), Vol. 1, pp 235-241. To date, three mammalian PPARs have been identified, namely PPAR-α, PPAR-γ, and PPAR-δ.

PPARs regulate expression of target genes by binding to DNA response elements as heterodimers with the retinoid X receptor. These DNA response elements have been identified in the regulatory regions of a number of genes encoding proteins involved in lipid metabolism and energy balance. The biological role of the PPARs in the regulation of lipid metabolism and storage has been recently reviewed. Spiegelman, Diabetes, (1998), Vol. 47, pp. 507-514; Schoonjans, *et al.*, Curr. Opin. Lipidol., (1997), Vol. 8, pp 159-166; Brun, *et al.*, Curr. Opin. Lipidol., (1997), Vol. 8, pp 212-218.

Molecules that interact with PPAR-γ may be useful in modulating PPAR-γ mediated processes for the treatment or prevention of various diseases and conditions. For example, essential dietary fatty acids and certain of their eicosanoid metabolites are naturally occurring hormonal ligands for the PPAR-γ receptor, which can promote adipogenesis through activation of the PPAR-γ receptor. Kliewer, *et al.*, Proc. Natl. Acad. Sci. USA, (1997), Vol. 94, pp 4318-4323; Kliewer, *et al.*, Cell, (1995), Vol. 83, pp 813-819. Therefore, molecules that inhibit the adipogenic effects of endogenous PPAR-γ hormones may be useful in the treatment of diseases caused by increased fat accumulation or lipid storage, such as osteoporosis, obesity and acne. Tontonoz, *et al.*, Curr. Opin. Genet. Dev., (1995), Vol. 5, pp 571-576. For example, it has been noted that the

thiazolidinedione (TZD) class of PPAR-γ ligands promotes adipogenesis in bone marrow and inhibits expression of markers of the osteoblast phenotype, such as alkaline phosphatase. Paulik, *et al.*, Cell Tissue Res., (1997), Vol. 290, pp 79-87. These effects may lead to low bone mineral density and osteoporosis. Similarly, it is known that TZDs can promote lipid accumulation in sebocytes. Rosenfield, *et al.*, N. Dermatology, (1998), Vol. 196, pp 43-46. These effects may lead to sebocyte differentiation and acne formation. Thus, molecules that block adipogenesis in adipocytes, pre-adipocytes, bone marrow, or sebocytes may have beneficial effects in the treatment of obesity, osteoporosis, or acne.

The PPAR-γ receptor has been found in tissues other than adipose, and it is believed that synthetic PPAR-γ ligands and natural PPAR-γ hormones (natural ligands) may have beneficial effects in many other diseases including cardiovascular disease, inflammation, and cancer. Schoonjans, *supra*; Ricote, *et al.*, Nature, (1998), Vol. 391, pp 79-82; Mueller, *et al.*, Mol. Cell, (1998), Vol. 1, pp 465-470.

TZD PPAR-γ ligands enhance the actions of insulin in man and reduce circulating glucose levels in rodent models of diabetes. The PPAR-γ receptor is expressed in adipose tissue and plays a pivotal role in the regulation of adipocyte differentiation *in vitro*. TZD such as rosiglitazone induce adipocyte differentiation *in vitro* through activation of the PPAR-γ receptor.

Although there are clearly therapeutic uses for PPAR-γ ligands in the treatment of diseases of lipid metabolism and energy balance, it is possible that there will be side effects of these drugs. For example, PPAR-γ ligands that promote adipocyte differentiation *in vivo* could lead to increased fat accumulation and weight gain. This side effect might offset the beneficial effects of a PPAR-γ ligand in the treatment of diabetes or other diseases where obesity is a risk factor. Spiegelman, *supra*; Brun, *supra*.

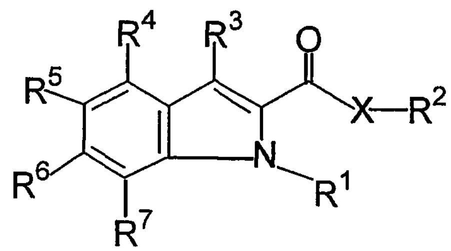
There is precedent among other member of the steroid/retinoid receptor superfamily that synthetic ligands can be identified which mimic many of the beneficial effects but inhibit some of the detrimental side effects of the natural hormones. McDonnell, Biochem. Soc. Trans., (1998), Vol. 26, pp 54-60. These synthetic ligands have been given various labels, including antagonists, anti-hormones, partial agonists, selective receptor modulators, tissue selective ligands, and others. Katzenellenbogen, *et*

al., Mol. Endocinol., (1996), Vol. 10, pp 119-131. Compounds are needed that will modulate PPAR-γ mediated processes for the treatment or prevention of diseases such as osteoporosis, cancer, *etc.* without the concommitant side-effects of natural hormones.

Summary of the Invention

The invention provides compounds that modulate PPAR-γ mediated processes, particularly substituted indole compounds, which can act as agonists or antagonists of PPAR-γ and thereby modulate PPAR-γ mediated processes. The invention further provides pharmaceutical compositions containing such compounds. Finally, the invention provides for methods of treating or preventing a PPAR-γ mediated diseases or condition in a mammal by administering a compound of the invention.

The invention relates to compounds of the Formula I:



(I)

wherein

R^1

is R^8-R^9;

R^8

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $(CH_2)_tS(=O)_2$, and $(CH_2)_nC(=O)$;

t

is 1-7;

n

is 0-8;

R^9

is selected from phenyl, cycloalkyl of 3-8 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^9 may be substituted with alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, halogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or Q-$(CH_2)_nR^{10}$;

Q

is selected from NR^{33}, NH, S and O;

R^{10}

is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

R^{33}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 1-8 carbon atoms and alkynyl of 1-8 carbon atoms;

X

is selected from NR^{33}, NH, O, and S;

R^2

is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, and $(CH_2)_nS(=O)_2R^{11}$;

R^{11}

is selected from aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, with the proviso that R^{11} is not isoxazole,

wherein R^{11} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

R^3

is selected from:

(a) R^{12}-R^{13}, wherein

R^{12}

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, and C(=O), and

R^{13}

is selected from cycloalkyl of 3-7 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{13} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; or

(b) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

all of which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, or may be spiro fused with cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-8 carbon atoms and 1-2 heteroatoms selected from N, S and O; or

(c) aryl of 5-14 carbon atoms or heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which are substituted with 1-3 of the following:

(i) $Si(CH_3)_3$;

(ii) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(iii) $S(=O)_2R^{14}$

wherein R^{14} is selected from cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(iv) R^{15},which combines with R^5 to form a radical of the formula $-Y-(CH_2)_t-$

Y-,

wherein Y is selected from NR^{33}, NH, S and O;

(v) $C(=O)R^{16}$,

- wherein R^{16} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $Z\text{-}R^{17}$,

- wherein Z is selected from $(CH_2)_n$, NH, NR^{33}, O and S,

- wherein R^{17} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(vi) $Z\text{-}R^{18}\text{-}R^{19}$, wherein:

- R^{18} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms, heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $(CH_2)_nC(=O)$, and

R^{19} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of

3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, R^{20}-R^{21} and Z-R^{21}, and

- Z is as defined above, and
- R^{20} is selected from aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{21} is selected from hydrogen, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

with the proviso that when R^3 is furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl R^3 may be unsubstituted, and

with the further proviso that, (1) when R^3 is aryl or heteroaryl, Z is O or $(CH_2)_n$, R^{18} is $(CH_2)_nC(=O)$, alkyl, aryl or heteroaryl, and R^{19} is hydrogen, halogen, haloalkyl or alkyl, or (2) when R^3 is phenyl or napthyl and R^{16} is alkyl, one of the following applies:

- R^5 is other than hydrogen and R^{23} is other than alkyl or alkenyl,
- X is NH and R^2 is $(CH_2)_nS(=O)_2R^{11}$,
- R^8 is $(CH_2)_nC(=O)$, $(CH_2)_tS(=O)_2$, alkenyl or alkynyl,
- R^9 is substituted with $Q(CH_2)_nR^{10}$,
- R^7 is other than hydrogen, or

- R^4 is other than hydrogen; and

(d) furyl, benzofuranyl, benzothienyl, benzoxazolidinyl, benzoxazolyl, benzothiazolydinyl, benzothiazolyl, benzoisothiazolyl, benzopyrazolyl, benzoimidazolyl, benzoimidazolidinyl, benzoisooxazolyl, or benzoxadiazolyl, which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen; or

R^4

is selected from hydrogen and E-R^{34}-R^{35},

wherein

E is selected from NR^{33}, NH, S and O;

R^{34} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

R^{35} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O; and

R^{33} has the meaning given above;

R^5

(1) is selected from:

(a) hydrogen;

(b) $(CH_2)_qCOOH$

where q is 1-4

(c) $C(=O)R^{22}$,

wherein R^{22} is selected from alkyl of 1-8 carbon atoms, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(d) cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(e) $-(CH_2)_n$-D-R^{23}, wherein:

(i) D is selected from NR^{33}, NH, S and O, and

(ii) R^{23} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)R^{24}$, and $(CH_2)_mR^{24}$, wherein

- m is 0-4, with the proviso that when R^3 is phenyl or napthyl, Z is O, R^{18} is alkyl and R^{19} is hydrogen, halogen, haloalkyl or alkyl, m is 1-4,

- R^{24} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, C(=O)OH, NHR^{27}-R^{28}, NR^{27}-R^{28}, $(CH_2)_nOR^{27}$-R^{28}, NH-R^{29}-R^{30} and R^{29}-R^{30},

- R^{27} is alkyl of 1-8 carbon atoms,

- R^{28} is selected from hydrogen, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{29} is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, aryl of 5-14 carbon atoms, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

- R^{30} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and C(=O)OH, or

(2) R^5 combines with R^6 to form a radical of formula -Y-$(CH_2)_t$-Y-,

wherein Y is as defined above;

R^6

is selected from hydrogen, OH, and T-R^{18}-R^{19},

wherein T is selected from NR^{33}, NH, S and O and R^{18}, R^{19} and R^{33} are as defined above;

R^7

is selected from hydrogen, $C(=O)R^{22}$, $(CH_2)_n$-D-R^{23}, and R^{31}-R^{32},

wherein D, R^{22} and R^{23} are as defined above, and

R^{31}

is selected from alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and C(=O), and

R^{32}

is selected from aryl of 5-14 carbon atoms, heteroaryl of 3-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

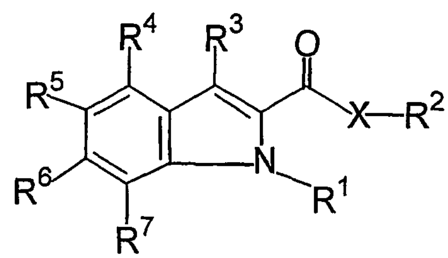
wherein R^{32} may be substituted with alkyl of 1-7 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

and pharmaceutically acceptable salts thereof.

The invention further relates to pharmaceutical compositions containing any of the above-described compounds of Formula I and a pharmaceutically acceptable carrier.

The invention also provides methods for treating or preventing a PPAR-γ mediated disease or condition in a mammal. The PPAR-γ mediated disease or condition may be osteopororsis, osteopenia, PPAR-γ mediated cancer, including breast, prostate, colon and lung cancer, inflammation, including atherosclerosis, inflammatory bowel disease, Alzheimer's disease and rheumatoid arthritis, hypertension, hyperglycemia, type 1 diabetes, type 2 diabetes, syndrome X, insulin resistance, obesity, dyslipidemia, hypertriglyceridemia, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, and skin disorders, such as acne, psoriasis, dermatitis, eczema, keratosis and inflammatory skin

conditions caused by lupus erythematosus. The methods of the invention provide for the administration of a compound of Formula I or a compound of Formula IIa:



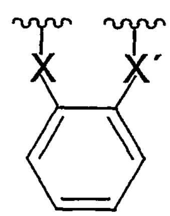
(IIa)

wherein

R^1

(1) is selected from hydrogen and R^8-R^9, or

(2) combines with R^7 to form a radical of the formula



R^8

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $(CH_2)_nS(=O)_2$ and $(CH_2)_nC(=O)$;

R^9

is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

wherein R^9 may be substitituted with alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, halogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or X-$(CH_2)_nCH_3R^{10}$,

R^{10}

is selected from cycloalkyl of 3-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkenyl of 5-9 carbon atoms, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O;

X and X′

are each independently selected from NH, NR^{33}, $(CH_2)_n$, O and S;

n

is a number from 0-8;

R^{33}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms and alkynyl of 2-8 carbon atoms;

R^2

is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, $NHS(=O)_2R^{11}$, and $(CH_2)_nS(=O)_2R^{11}$;

R^{11}

is selected from aryl of 5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{11} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

R^3

is selected from:

(a) hydrogen,

(b) R^{12}-R^{13}, wherein

R^{12}

is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and $(CH_2)_nC(=O)$,

R^{13}

is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

wherein R^{13} may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

(c) cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, all of which may be:

(i) substituted with aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and $C(=O)(CH_2)_nCH_3$, or

(ii) fused with a spiro ring of 1-6 carbon atoms, or

(iii) fused with an aryl of 5-14 carbon atoms or a heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, either of which may be substituted with alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, or halogen;

(d) aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, either of which may be substituted with:

(i) $-Si(CH_3)_3$;

(ii) $S(=O)_2R^{14}$,

wherein R^{14} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(iii) R^{15}, which combines with R^5 to form a radical of the formula $-Y-(CH_2)_n-Y-$,

wherein Y and n are as defined above;

(iv) $C(=O)R^{16}$,

- wherein R^{16} is selected from alkyl of 1-8 carbon atoms and $X-R^{17}$
- wherein R^{17} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- wherein X is as defined above;

(v) $X-R^{18}-R^{19}$

- R^{18} is selected from alkyl of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{19} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, R^{20}-R^{21} and X-R^{21},
- X is as defined above,
- R^{20} is aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and
- R^{21} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

R^4

is selected from hydrogen and X-R^{18}-R^{19},

wherein X, R^{18} and R^{19} have the meanings given above;

R^5

(1) is selected from:

(a) hydrogen;

(b) R^{12}-R^{13},

wherein R^{12} and R^{13} are as defined above,

(c) $C(=O)R^{22}$, wherein

R^{22} is selected from alkyl of 1-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(d) alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(e) $-(CH_2)_n$-Y-R^{23}, wherein:

(i) Y and n are as defined above,

(ii) R^{23} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)R^{24}$, $(CH_2)_nR^{24}$, and R^{25}-R^{26}, wherein

- R^{25} is alkyl of 1-8 carbon atoms,
- R^{26} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O,

- R^{24} is selected from cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, C(=O)OH, NHR^{27}-R^{28}, NR^{27}-R^{28}, $NR^{33}R^{27}$-R^{28}, $(CH_2)_nR^{27}$-R^{28}, and R^{29}-R^{30},

- R^{27} is alkyl of 1-8 carbon atoms,

- R^{28} is selected from hydrogen, aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, all of which, with the exception of hydrogen, may be fused with aryl of 5-14 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected N, S and O,

- R^{29} is selected from aryl of 5-14 carbon atoms, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, cycloalkyl of 3-9 carbon atoms, cycloalkenyl of 5-9 carbon atoms, heterocycloalkyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heterocycloalkenyl of 3-8 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

- R^{30} is selected from hydrogen, halogen, haloalkyl of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of

5-14 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(2) combines with R^6 to form a radical of the formula $-Y-(CH_2)_n-Y-$,

wherein Y and n have the meanings given above;

R^6

is selected from hydrogen, OH and $X-R^{18}-R^{19}$,

wherein X, R^{18} and R^{19} have the meanings give above

R^7

is selected from hydrogen, $C(=O)R^{22}$, $(CH_2)_n-Y-R^{23}$, and $R^{12}-R^{13}$,

wherein R^{22}, R^{23}, R^{12}, R^{13}, Y and n have the meanings give above;

and pharmaceutically acceptable salts thereof.

The present invention therefore provides compounds, pharmaceutical compositions containing such compounds, and methods for the treatment or prevention of PPAR-γ mediated diseases and conditions. Compounds, compositions and methods of the present invention therefore are useful in treatment of PPAR-γ mediated diseases and conditions without the concommitant undesired side-effects of natural hormones. These and other aspects of the invention will be more apparent from the following description and claims.

Detailed Description of the Invention

The invention provides novel, substituted indoles of Formula I, pharmaceutical compositions containing such indoles, and their use in the treatment or prevention of PPAR-γ mediated diseases or conditions in a mammal. The invention further provides methods of treating or preventing PPAR-γ mediated diseases or conditions in a mammal, such as a human, by administration of a compound of Formula IIa. The compounds of Formula I and Formula IIa have both been broadly described above.

In one embodiment of the compounds of Formula I:

R^8 is alkyl

R^9 is phenyl, which may or may not be substituted;

X is O;

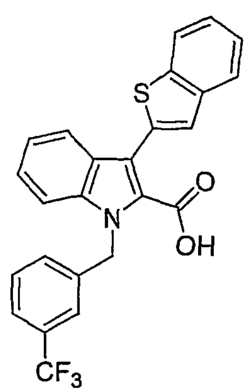
R^2 is hydrogen; and

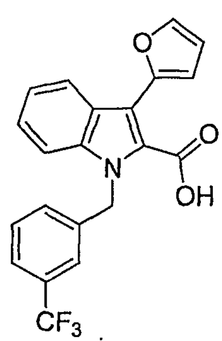
R^3 is aryl, particularly phenyl, or heteroaryl, either of which may or may not be substituted.

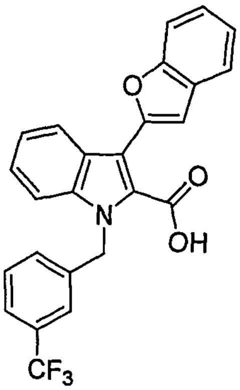
As used herein, the term "aryl" includes aromatic ring structures that are substituents on another atom. These aryls may also be substituted with substituents, such as halogen, haloalkyl, alkoxy, haloalkoxy, *etc.* Non-limiting examples of aryls include phenyl, napthyl, *etc.* Likewise, the term "heteroaryl" as used herein includes aromatic ring structures containing between one and two heteroatoms, such as O, N and S, that are substituents on another atom. These heteroaryls may also be substituted with substituents, such as alkyl, alkenyl, alkoxy, haloalkoxy, halogen, haloalkyl, *etc.* Non-limiting examples of heteroaryls include pyridyl, furyl, quinolyl, *etc.*

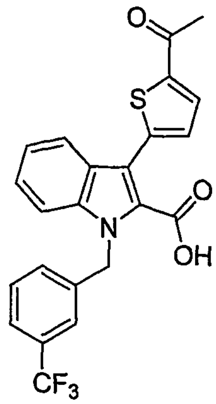
As used herein the term "alkyl" includes straight-chain or branched alkyls of between 1 and 8 carbon atoms. The term "alkenyl" includes straight-chain or branched alkenyls of between 2 and 8 carbon atoms. As used herein the term "alkynyl" includes straight-chain or branched alkynyls of between 2 and 8 carbon atoms. Such alkyls, alkenyls and alkynyls may be terminal or may be linkers between other portions of a molecule.

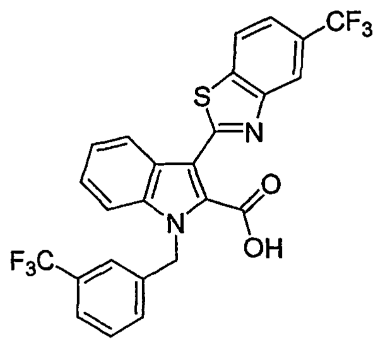
Examples of compounds of the invention where R^3 is a heteroaryl include, but are not limited to:

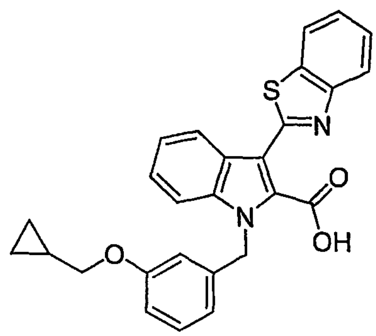


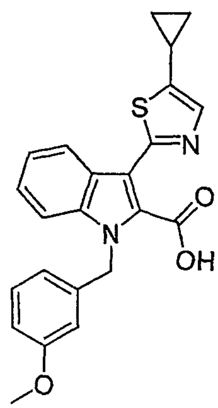


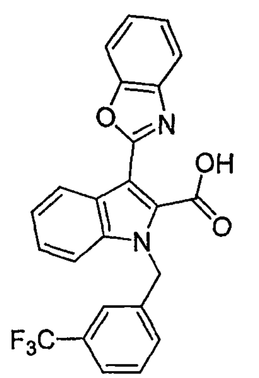


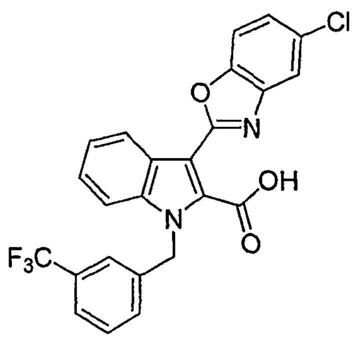


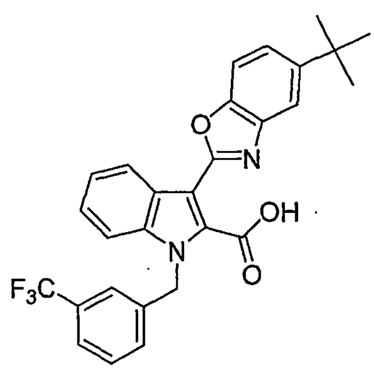


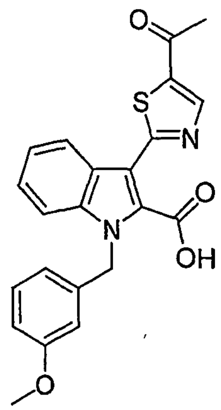




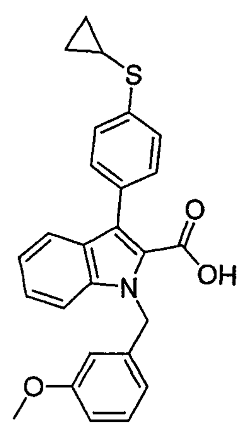


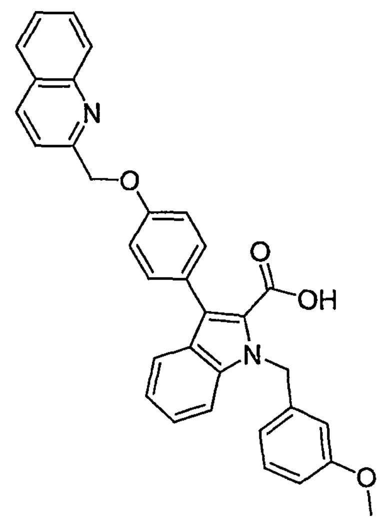


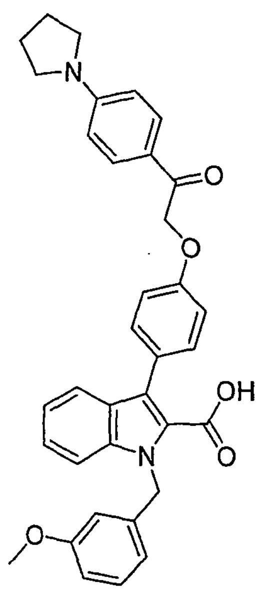


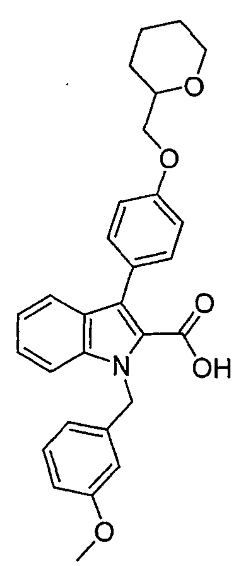


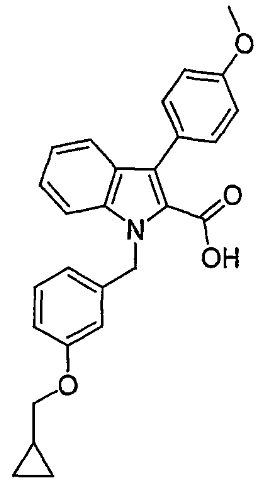
Examples of compounds of the invention where R^3 is phenyl include, but are not limited to:











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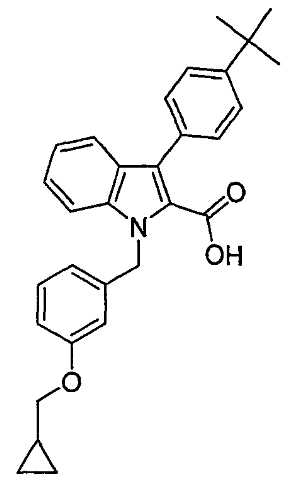
N
O



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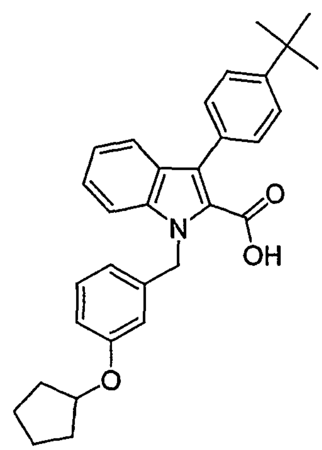

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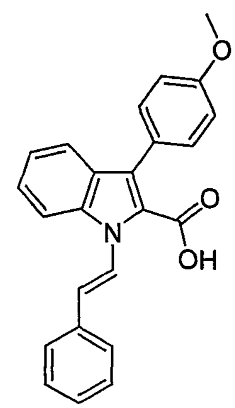

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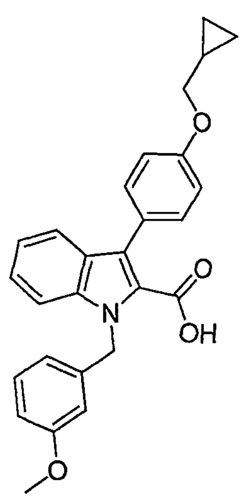

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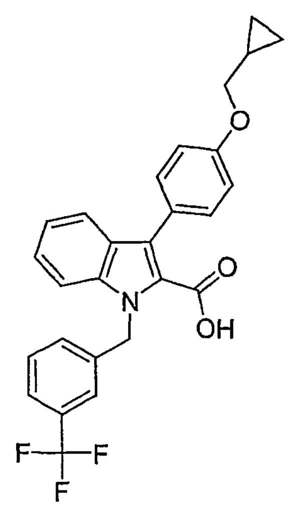

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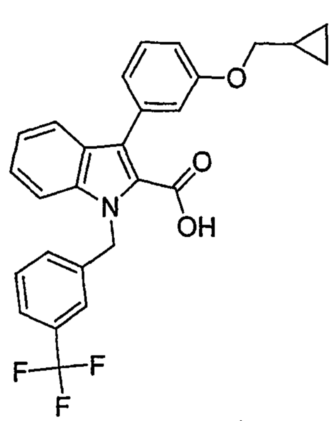
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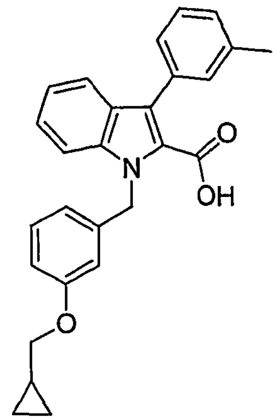
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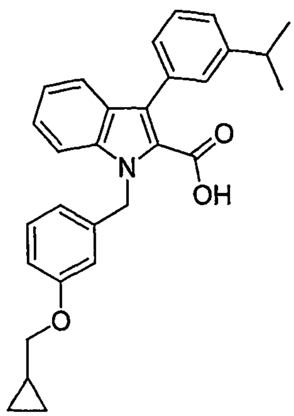
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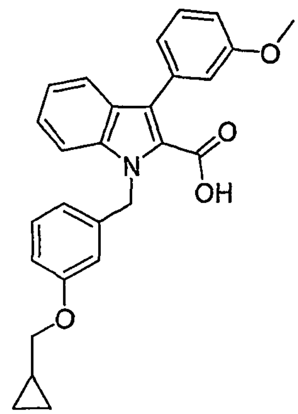
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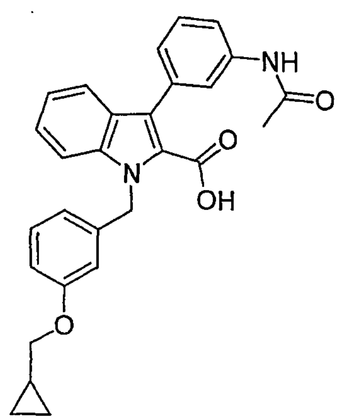
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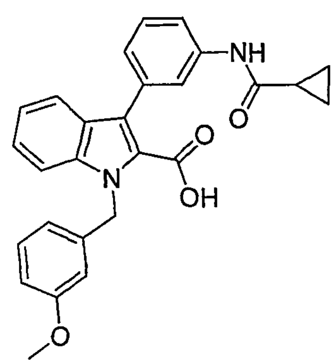
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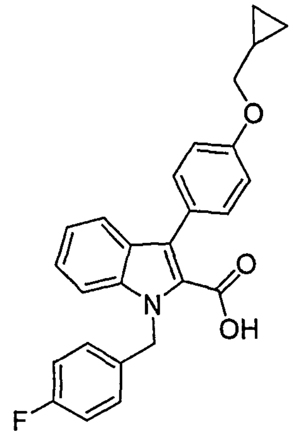
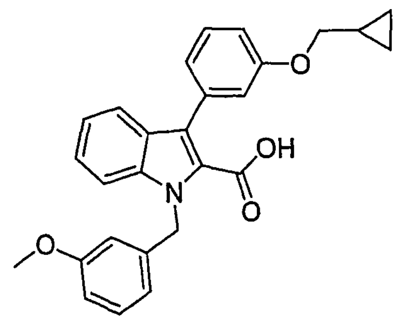
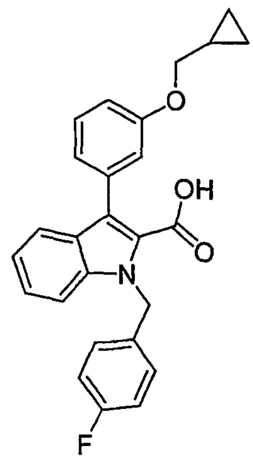
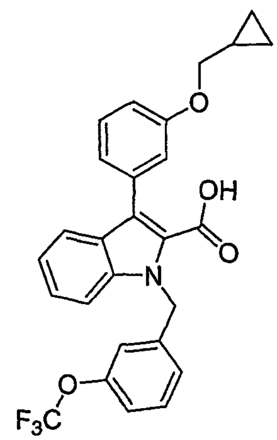
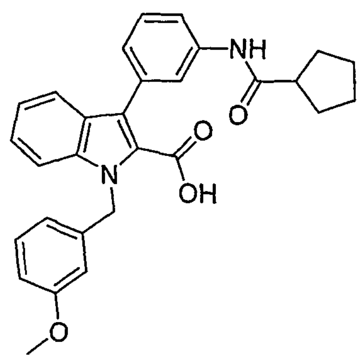
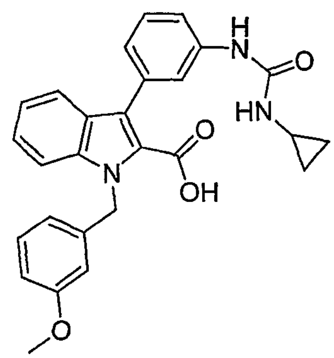


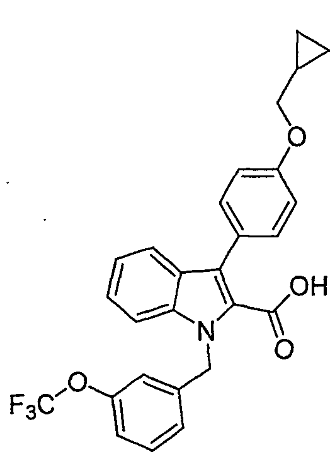


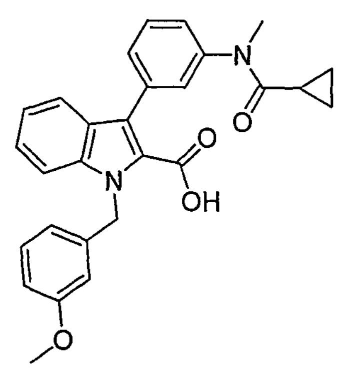


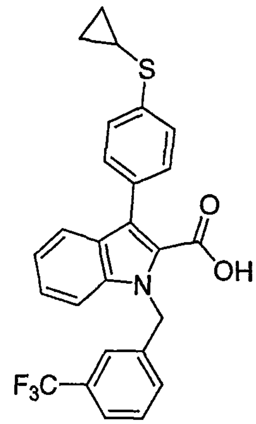




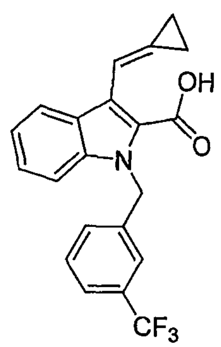


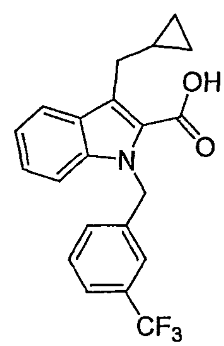


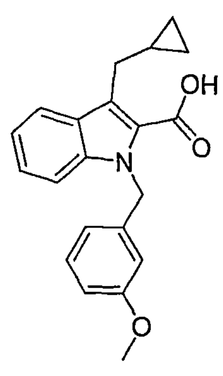


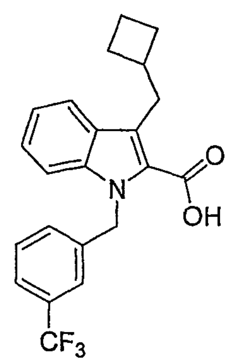


In another embodiment of the invention, R^3 is R^{12}-R^{13}, where R^{13} is cycloalkyl, heterocycloalkyl, cycloalkenyl or heterocycloalkenyl. Examples of compounds of the invention where R^3 is R^{12}-R^{13} include, but are not limited to:

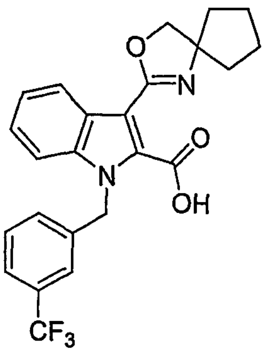


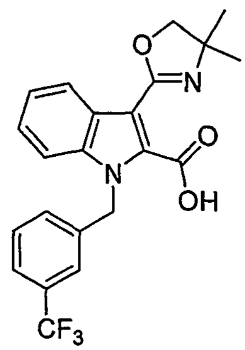




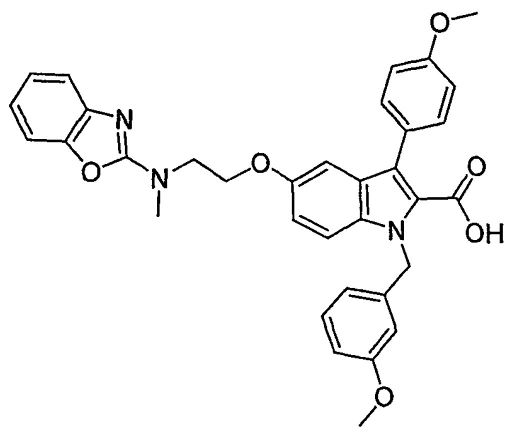


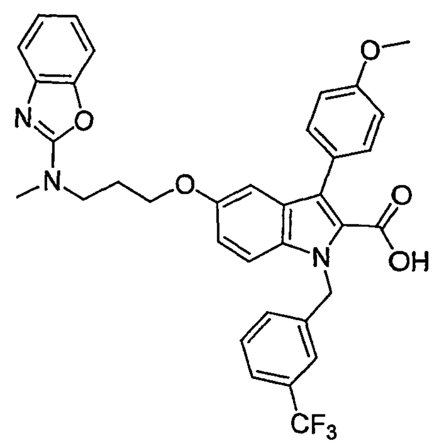
In other embodiments of the invention, R^3 is a cycloalkyl, heterocylcoalkyl, cycloalkenyl or heterocycloalkenyl, which may be substituted or may be fused with a spiro ring of 3-9 carbon atoms. Examples of compounds of the invention where R^3 is a cycloalkyl, heterocylcoalkyl, cycloalkenyl or heterocycloalkenyl include, but are not limited to:

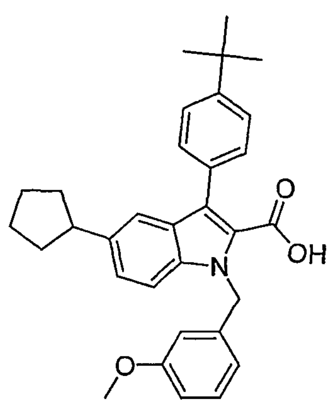


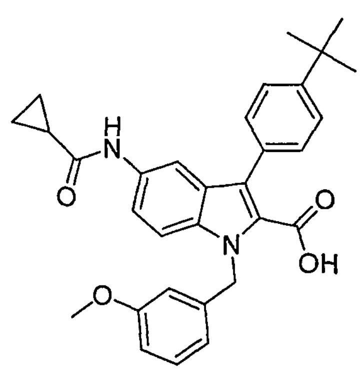


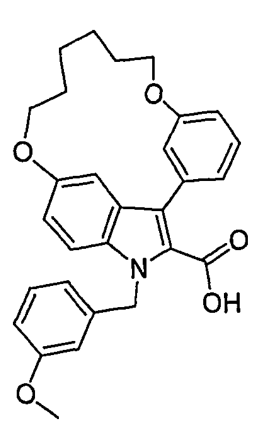
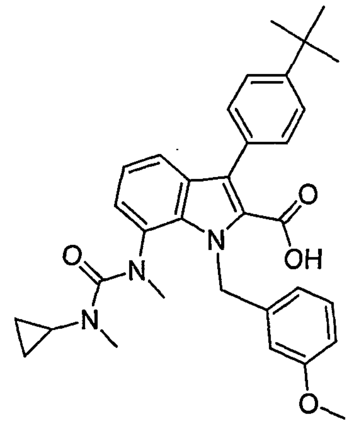
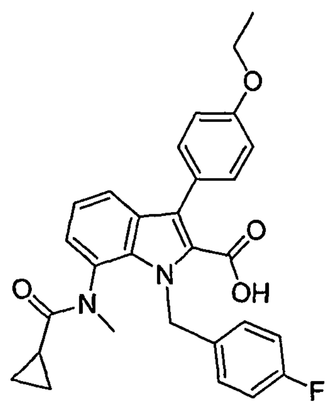
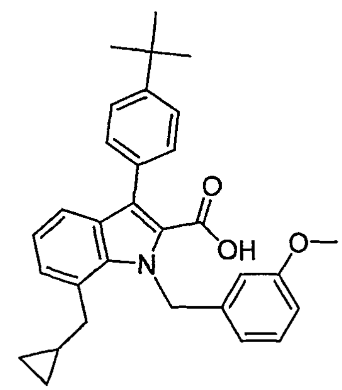
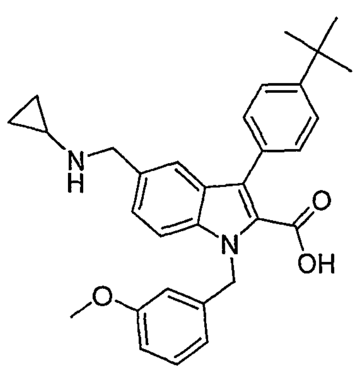
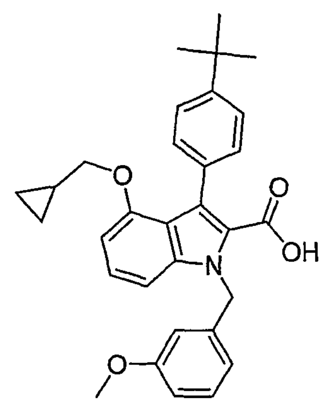
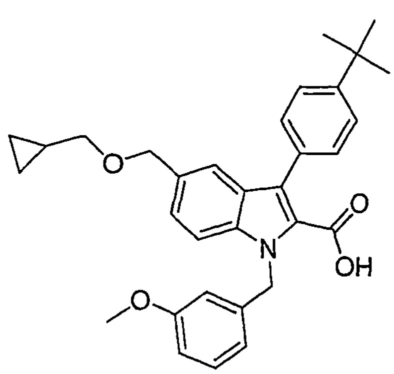
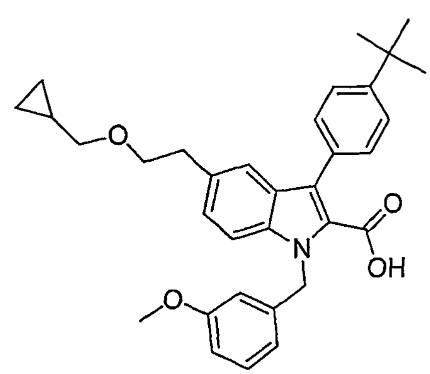
In still other embodiments of the invention, R^4, R^5, R^6 and/or R^7 may be other than hydrogen. Examples of compounds of the invention where R^4, R^5, R^6 and/or R^7 are other than hydrogen include, but are not limited to:

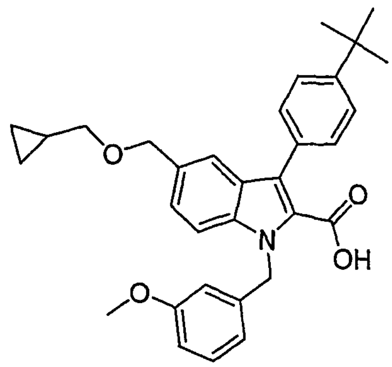










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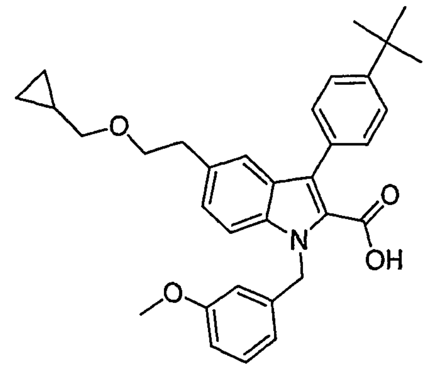

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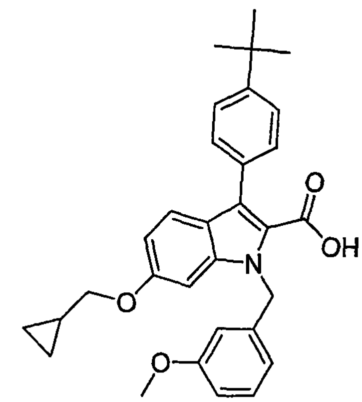

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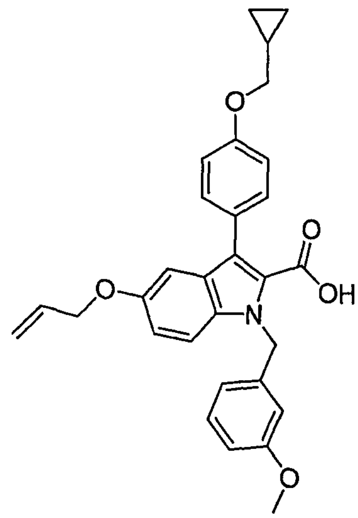

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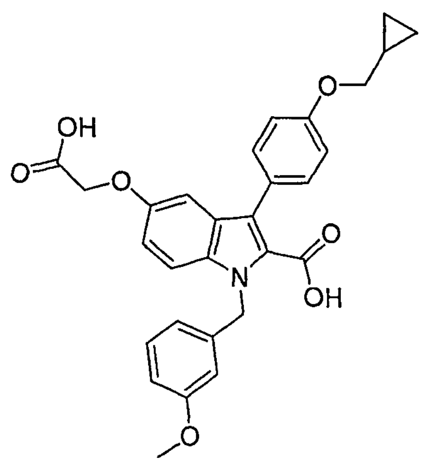

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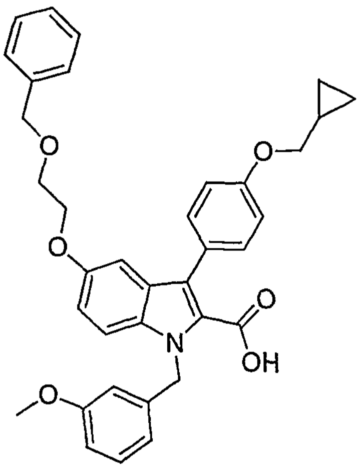

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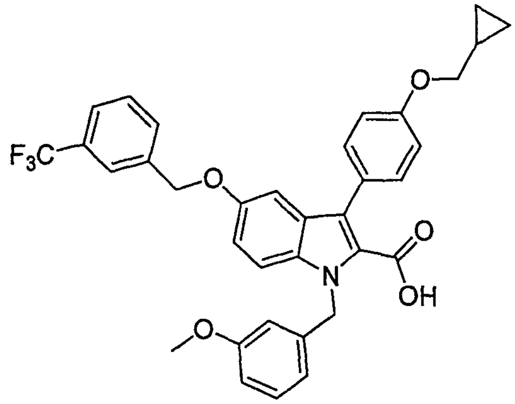
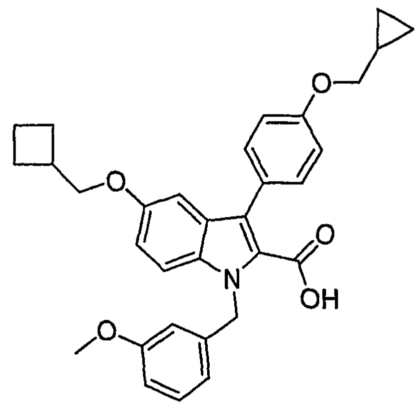




Compounds of Formulas I and IIa may be useful in the treatment or prevention of PPAR-γ mediated diseases or conditions. An agent which binds to PPAR-γ may be employed for a wide variety of indications, including, but not limited to:

(1) osteoporosis and osteopenia, *see,* Nuttall, *et al.*, Bone 27 (2), (2000), 177-184; Gimble, *et al.*, Bone 19 (5), (1996), 421-428;

(2) cancer, particularly PPAR-γ mediated cancers, such as breast and prostate cancers (*see,* Gelman, *et al.*, Cell. and Mol. Life Sci., 55 (6-7), (1999), 935-943; Kersten, *et al.*, Nature, 405 (6785), May 25, 2000, 421-424), colon cancer (*see*, Saez, *et al.*, Nat. Med., 4 (9) Sept. 1998, 1058-1061; Lefebvre, *et al.*, Nat. Med., 4 (9), Sept. 1998, 1053-1057; Demetri, *et al.*, Proc. Nat'l. Acad. Sci. USA, 96 (7), Mar. 30, 1999, 3951-3956) liposarcoma (Demetri, et al., Proc. Nat'l. Acad. Sci USA, 96 (7), Mar. 30, 1999, 3951-3956) and lung cancer (*see*, Chang, *et al.*, Cancer Res., 60, 2000, 1129-1138);

(3) hyperglycemia, type 1 diabetes, type 2 diabetes, syndrome X, and insulin resistance, (*see* Lehmann, *et al.*, J. Bio. Chem., 270 (22) (1995), 12953-12956; Spiegelman, Diabetes, 47 (4), (1998), 507-514);

(4) obesity, (*see* Zhou, *et al.*, Proc. Nat'l. Ac. Sci. USA, 96 (5), (1999), 2391-2395; U.S. Patent No. 6,033,656);

(5) inflammation, particularly inflammatory bowel disease (*see* Cell. and Mol. Life Sci., 55 (6-7), (1999), 935-943), Alzheimer's disease (*see*, Combs, *et al*, J. Neurosci. 20 (2), 2000, 558-567), rheumatoid arthritis (*see*, Jiang, *et al.*, Nature 391 (6662), 1998, 82-86), and atherosclerosis (*see* Pasceri, *et al.*, Circulation, 101 (3), 2000, 235-238);

(6) cardiovascular disease, particularly hypertension, (*see* Cell. and Mol. Life Sci., 55 (6-7), (1999), 935-943 review);

(7) dyslipidemia, hypertriglyceridemia, diabetic dyslipidemia, hyperlipidemia and hypercholesteremia (*see* Hulin, *et al.*, Curr. Pharm. Design, 2 (1996), 85-102); and

(8) skin disorders, particularly inflammatory skin disorders caused by lupus erythematosus, and acne, psoriasis, dermatitis, eczema and keratosis (*see*, WO 99/34783; U.S. Patent No. 5,981,586).

Compounds of Formulas I and IIa are preferably used in the treatment or prevention of osteopenia, osteoporosis, and PPAR-γ mediated cancers, including breast, prostate and colon cancer.

The present invention also includes pharmaceutically acceptable salts of the compounds of Formulas I and IIa. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (*e.g.*, Li^{+} Na^{+} or K^{+}), alkaline earth cations (*e.g.*, Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary

ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

A number of the compounds of Formulas I and IIa possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to the skilled in the art. The present invention encompasses any racemic or optically active forms of compounds described in Formula I or Formula IIa which possess PPAR-γ modulating activity or the use of any racemic or optically active forms of the compounds described in Formulas I and IIa for the treatment or prevention of PPAR-γ mediated diseases or conditions.

The therapeutic agents of the invention may be employed alone or concurrently with other therapies. For example, when employed as a treatment for osteoporosis or osteopenia, the compounds of the invention may be used in combination with a calcium source, vitamin D or analogues of vitamin D, and/or antiresorptive therapies such as estrogen replacement therapy, treatment with a fluoride source, treatment with calcitonin or a calcitonin analogue, or treatment with a bisphosphonate such as alendronate. The method of the invention is intended to be employed for treatment of PPAR-γ mediated diseases or conditions in both humans and other mammals.

The compounds may be administered orally, dermally, parenterally, by injection, by inhalation or spray, or sublingually, rectally or vaginally in dosage unit formulations. The term "administered by injection" includes intravenous, intraarticular, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and, if desired, other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already

mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, *e.g.*, oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of the invention may also be administered transdermally using methods known to those skilled in the art (*see, e.g.*, Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp *et al.* WO 94/04157 3Mar94). For example, a solution or suspension of a compound of Formula I or IIa in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with

additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I or IIa may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery systems are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C_8-C_{18} fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C_8-C_{18} fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl isobutyl *tert*-butyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbid and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C_8-C_{18} fatty alcohols, saturated or unsaturated C_8-C_{18} fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers,

styrene-butadiene coploymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

For all regimens of use disclosed herein for compounds of Formulas I and IIa, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, *i.e.*, the mode of treatment and the daily number of doses of a compound of Formula I or IIa or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

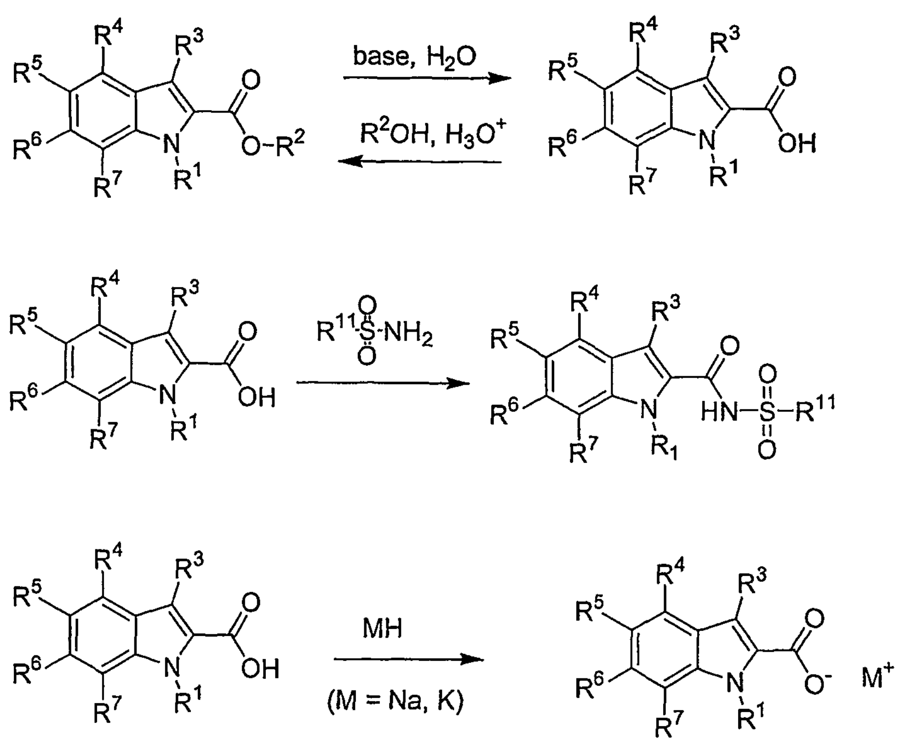
The compounds of Formulas I and IIa may be prepared by use of known chemical reactions and procedures, from known compounds (or from starting materials which, in turn, are producible from known compounds) through the preparative methods shown below, as well as by other reactions and procedures known to the skilled in the art. Such reactions and procedures include, but are not limited to, esterification, hydrolysis, alkylation, acylation neutralization, coupling, oxidation, reduction, condensation,

elimination and substitution reactions. Nevertheless, the following general preparative methods are presented to aid practitioners in synthesizing the compounds of the invention, with more detailed particular examples being presented in the experimental section. The examples are for illustrative purposes only and are not intended, nor should they be construed, to limit the invention in any way.

Within the scope of each method, optional substituents may appear on reagents or intermediates which may act as protecting groups or other non-participating groups. Utilizing methods well known to those skilled in the art, such groups are introduced and/or removed during the course of the synthetic schemes to provide the compounds of the present invention. All variable groups not defined below are as described hereinabove.

In general, compounds of Formula I or IIa may be prepared from the appropriately substituted indoles, by esterification, hydrolysis, sulfonylation or neutralization reactions as shown in Flow Diagram I:

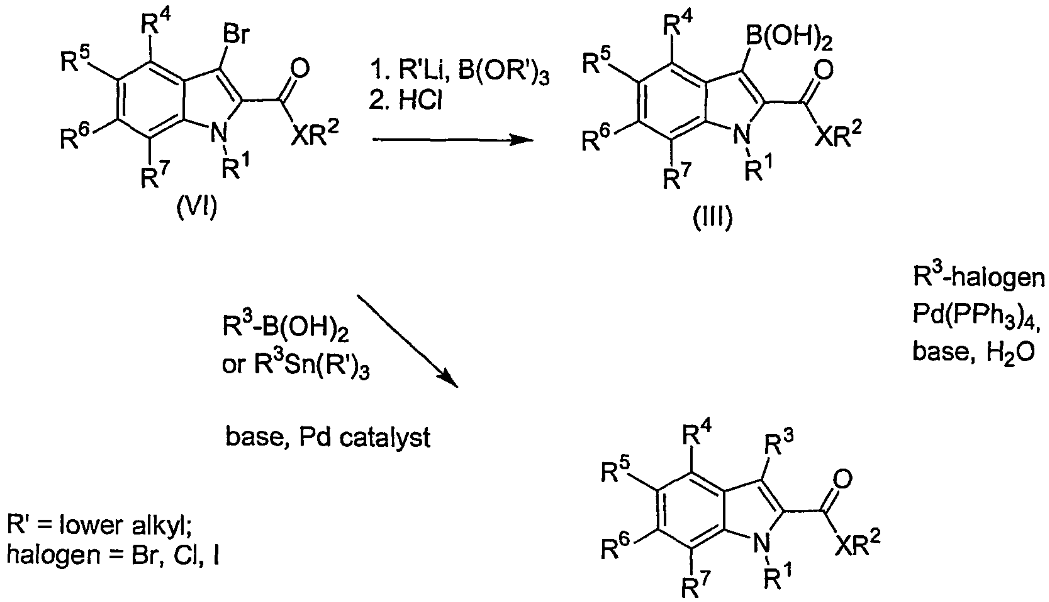
Flow Diagram I



Preparation of certain Formula I compounds with a variety of R^3 substituents may be prepared by a sequence involving conversion of VI to a boronic acid intermediate,

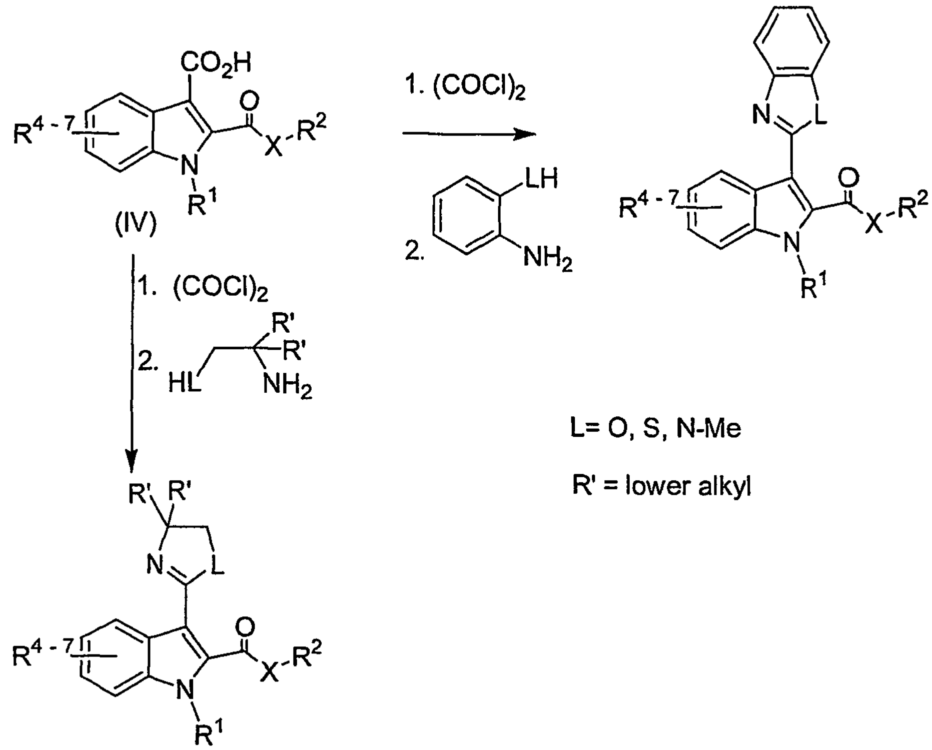
followed by a palladium-facilitated coupling reaction with an organohalide and base, such as triethylamine, potassium carbonate or Huenig's base, as shown in Flow Diagram II. Alternatively, either a boronic acid or organotin intermediate may be coupled with VI under similar conditions.

Flow Diagram II



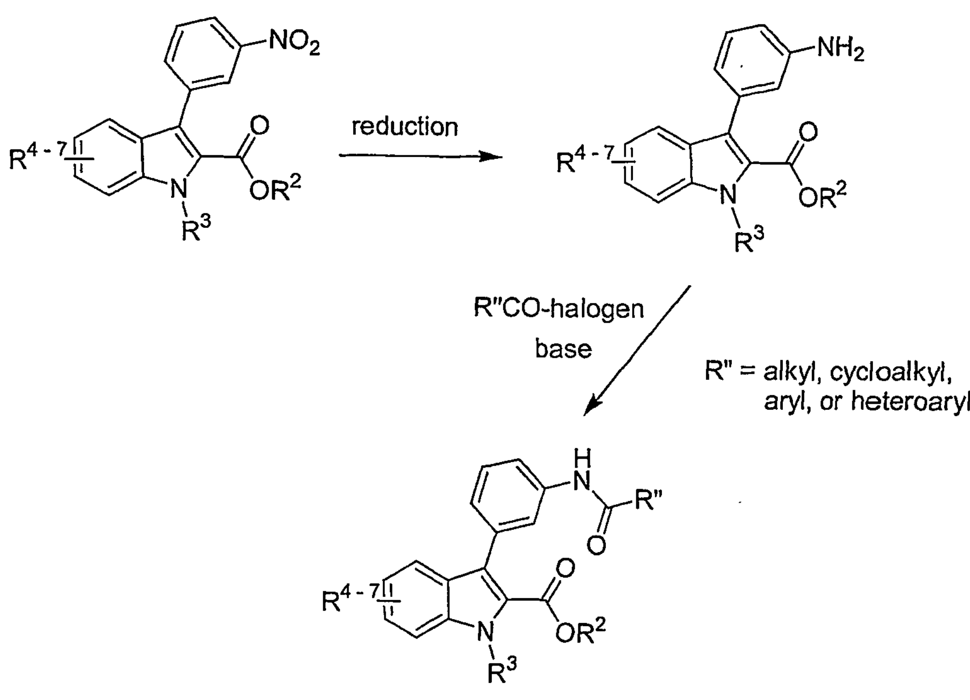
Other compounds with heterocycloakenyl or heteroaryl substituents at the R^3 position may prepared by condensation of 3-carboxy-substituted indoles with 2-aminoethanols, 2-aminophenols or 2-aminothiols as illustrated in Flow Diagram III.

Flow Diagram III



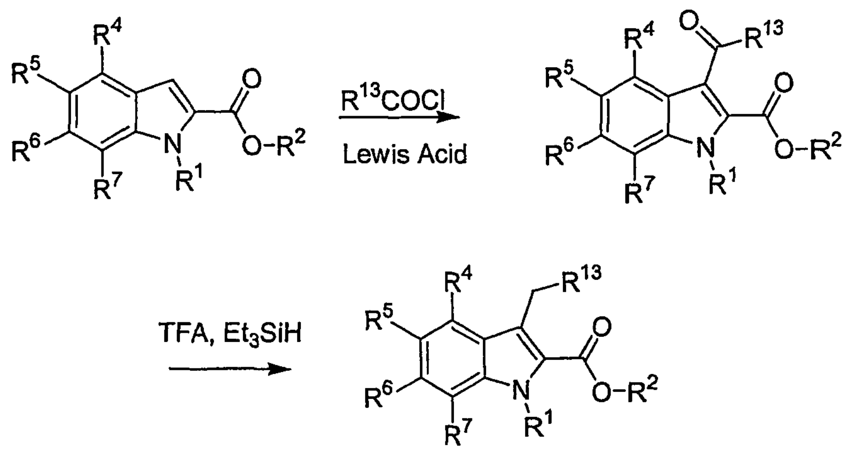
Certain aryl substituents on the R^3 aryl ring may be further transformed to other substituents by standard means. An illustration of this is shown in Flow Diagram IV, in which a nitro group is reduced and acylated to provide amido substituents.

Flow Diagram IV



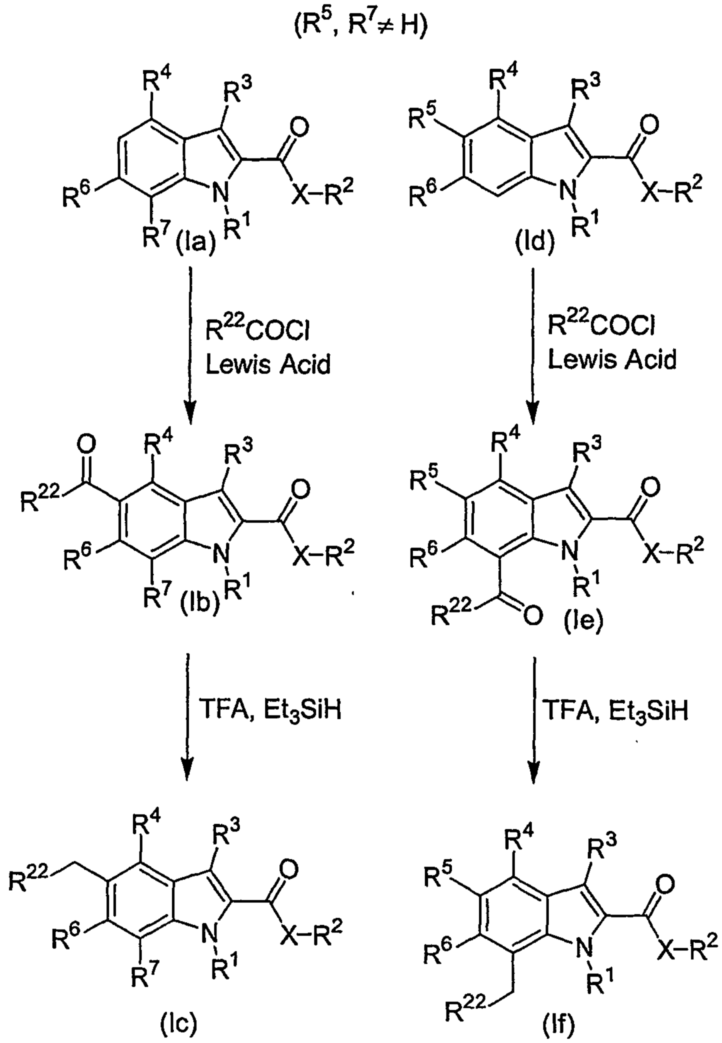
Compounds of Formula I which bear certain R^3 substituents may be prepared by Friedel-Crafts acylation of the corresponding unsubstituted indole, followed by reduction of the carbonyl group to a methylene, as shown in Flow Diagram V.

Flow Diagram V

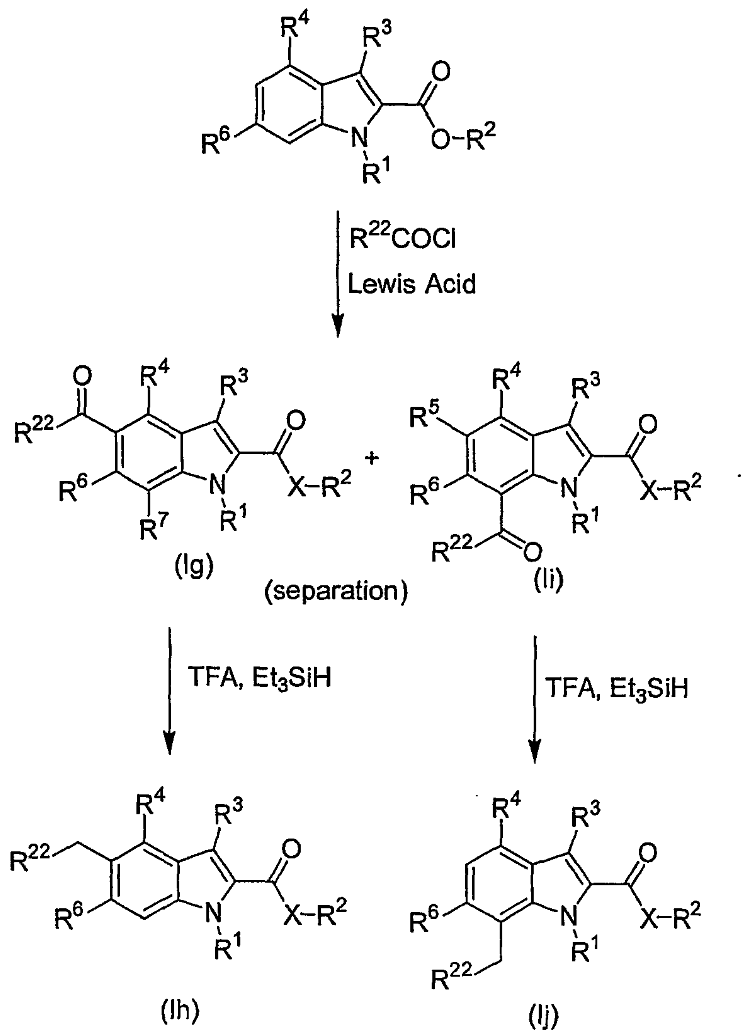


Compounds of Formula I with similar substituents at either R^5 or R^7 may be likewise prepared, either individually (Flow Diagram VI) or as mixtures (Flow Diagram VII) by an analogous sequence of acylation and reduction reactions. In the latter scheme, where R^5 and R^7 are hydrogen in the starting materials, individual compounds may be obtained by chromatographic separation of products (Ig and Ii) after the initial step.

Flow Diagram VI

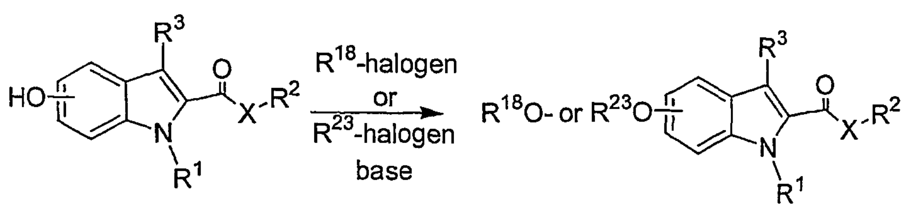


Flow Diagram VII



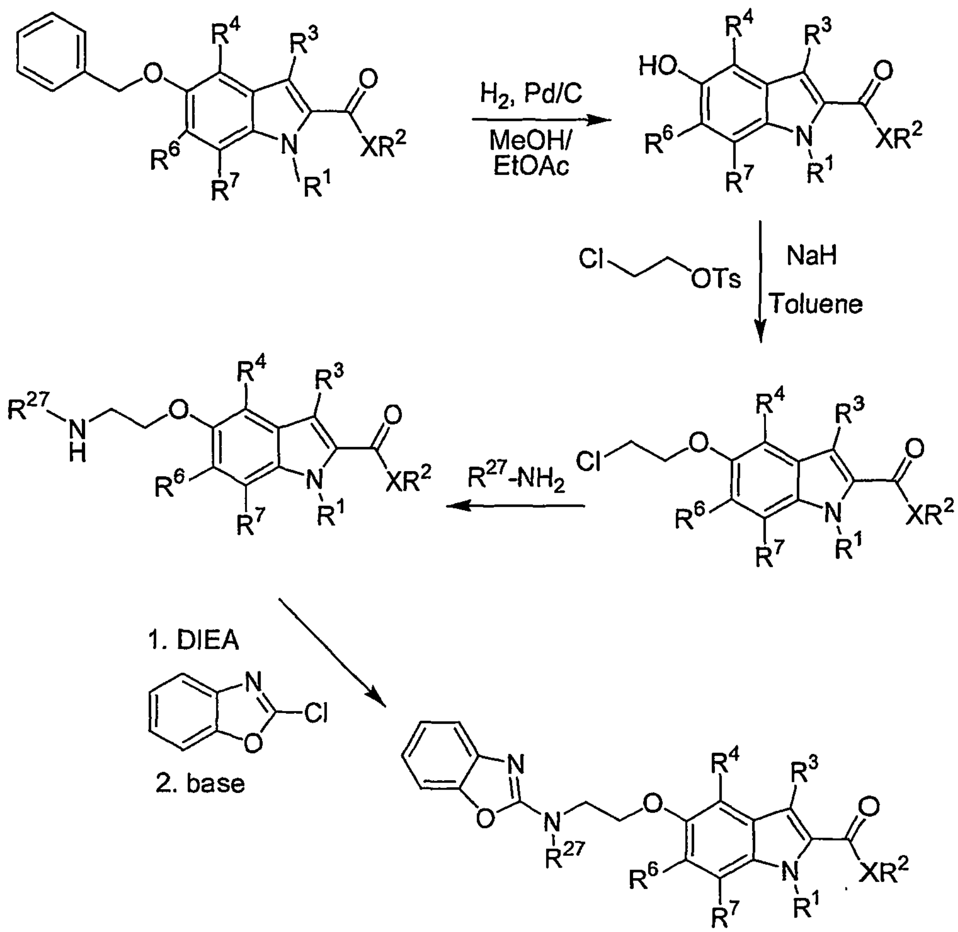
O-Alkylation reactions may be utilized to prepare Formula I compounds bearing substituents on R^4, R^5, R^6 or R^7 positions. For example, alkylation of the corresponding hydroxy intermediates provides ethers containing an R^{18} or R^{23} group, depending upon position, as shown in Flow Diagram VIII.

Flow Diagram VIII



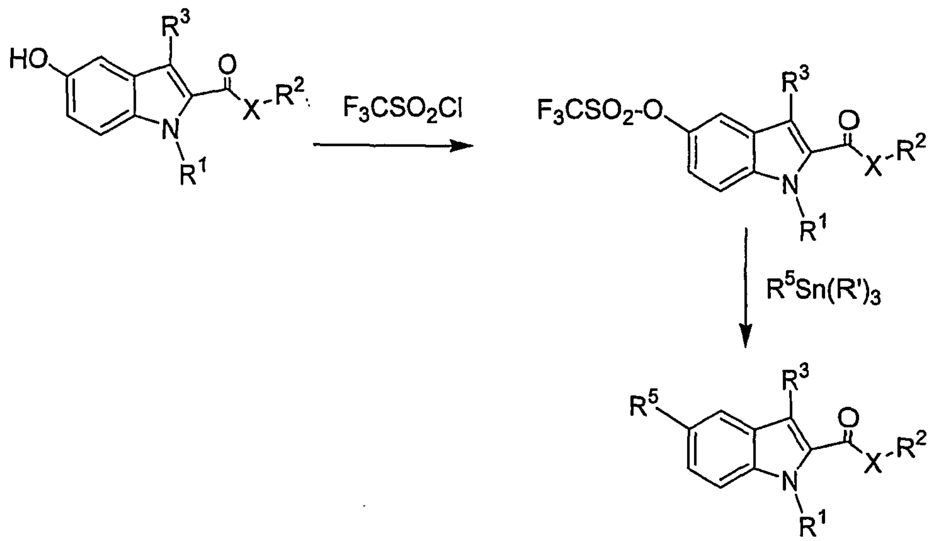
A more detailed example of this process is shown for compounds bearing R^5 the group in Flow Diagram IX.

Flow Diagram IX



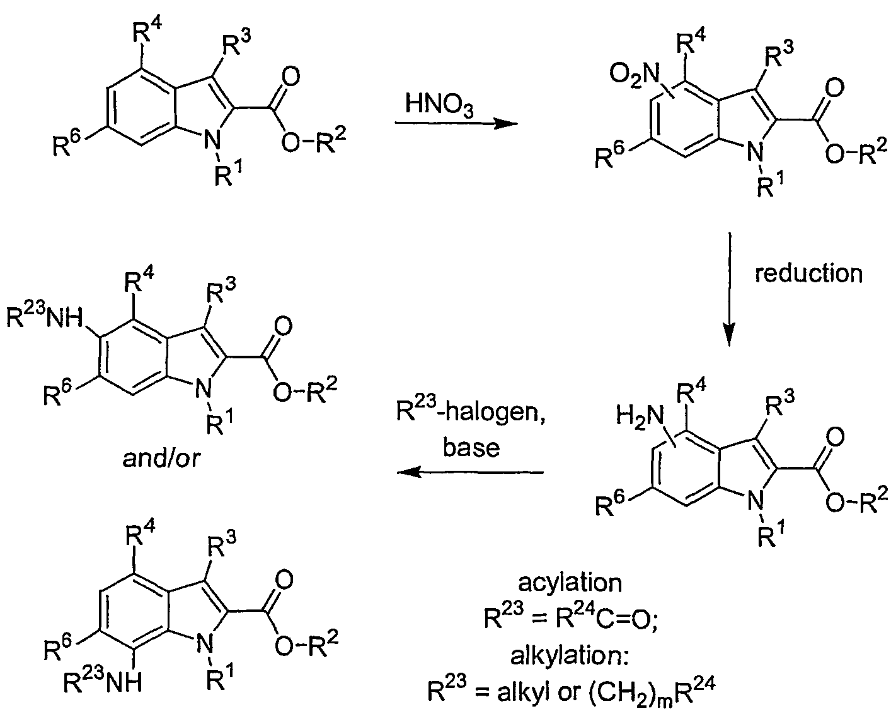
Other compounds of Formula I may also be obtained from a hydroxy intermediate. For example, the hydroxy group may be converted to a trifluoromethylsulfonate which reacts with an alkyl stannane to give alkyl-substituted indoles, as exemplified in Flow Diagram X for the R^5 position.

Flow Diagram X



Nitration of indoles that are unsubstituted at positions 5 and/or 7 provides nitro-substituted intermediates which may be reduced and either acylated or alkylated to give a variety of Formula I compounds as shown in Flow Diagram XI.

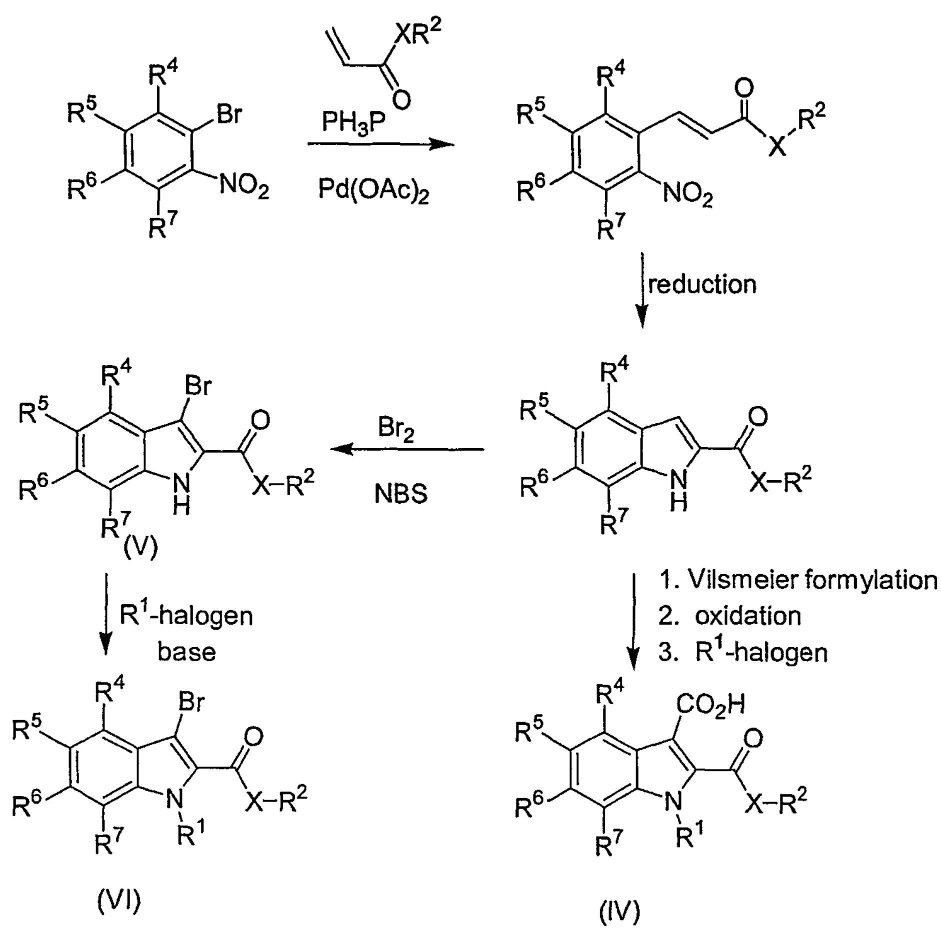
Flow Diagram XI



Indole intermediates which are useful in the preparation of compounds in the present invention are either commercially available or may be prepared by standard methods. These transformations are summarized in Flow Diagram XII for intermediates

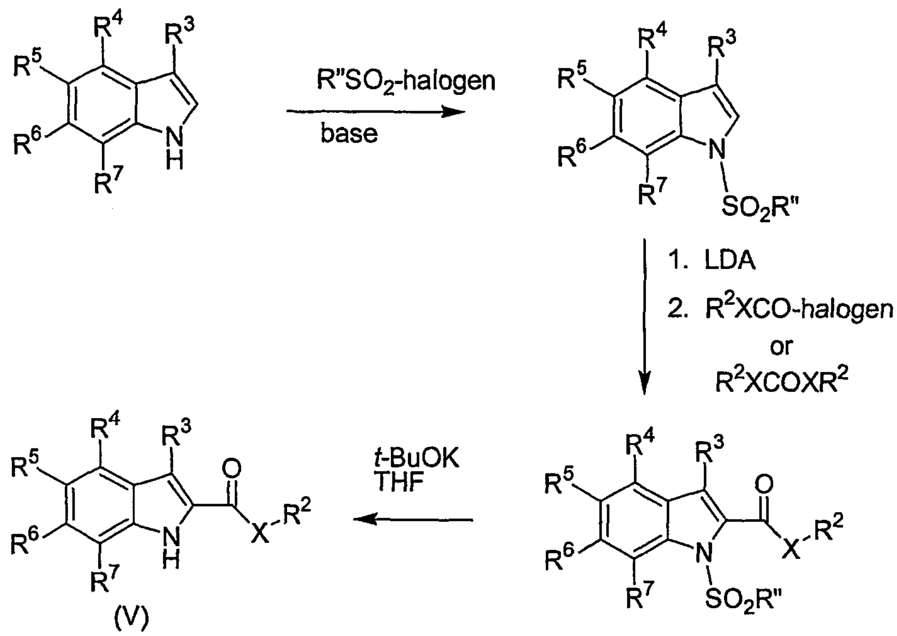
of Formula VI, IV and V. For example, an appropriately substituted 2-bromonitrobenzene may be converted to a 2-nitrocinnamic acid derivative which cyclizes to an indole upon reduction. The resulting indole intermediate may then be brominated at the 3 position, and the desired R^1 substituent introduced by N-alkylation giving the intermediate compounds of Formula VI. Compounds of Formula IV may be prepared from VI in a stepwise sequence involving halogen-metal exchange, addition to formaldehyde, and oxidation of the resulting carbinol to a 3-carboxylic acid. It is understood that the presence of certain R^4-R^7 substituents may require additional steps of protection and deprotection during this process in order to avoid undesired side reactions.

Flow Diagram XII



The introduction of the carboxyl functionality at position 2 of other indole compounds may be accomplished by a sequence shown in Flow Diagram XIII. The nitrogen of the unsubstituted indole is first protected as a sulfonamide, then subjected to acylation conditions catalyzed by Lewis acid. Protection may be then be removed and the desired R^1 attached as described above.

Flow Diagram XIII



Preparative Examples

Examples of preparations of both intermediates and compounds of the invention are provided in the following detailed synthetic procedures. In the tables of compounds to follow, the synthesis of each compound is referenced back to these exemplary preparative steps. All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by volume.

All reactions were performed under a positive pressure of dry argon, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. Thin-layer chromatography (TLC) was performed on Whatman® pre-coated, glass-backed silica gel 60A F-254 250 μm plates. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel. Melting points (mp) were determined using a Thomas-Hoover melting point apparatus, an Electrothermal melting point apparatus, or a Mettler FP66 automated melting point apparatus and are uncorrected.

^{1}H-NMR spectra were recorded with a Varian Mercury (300 MHz,) or a Bruker Avance 500 (500 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated

solvent ($CDCl_3$ δ 7.26; CD_3OD δ 3.30; DMSO-D_6 δ 2.49; Acetone-D_6 δ 2.04; or CD_3CN δ 1.94).

HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a YMC Pro C18 2.0 mm x 23 mm column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Gradient elution from 90% A to 95% B over 4 minutes was used on the HPLC. Buffer A was 98% water, 2% Acetonitrile and 0.02% TFA. Buffer B was 98% Acetonitrile, 2% water and 0.018% TFA. Spectra were scanned from 140-1200 amu using a variable ion time according to the number of ions in the source.

Fourier transform infrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer.

Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. NMR mass and infrared spectra, and elemental analyses of the compounds were consistent with the assigned structures.

List of Abbreviations and Acronyms

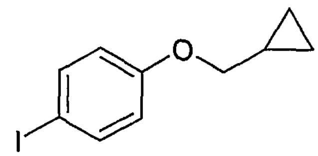
As employed herein, the following terms have the indicated meanings.

Ac_2O	acetic anhydride
AIBN	2,2'-azobisisobutyronitrile
anh	anhydrous
aq	aqueous
BOC	*tert*-butoxycarbonyl
BuLi	*n*-butyllithium
calc'd	calculated
Celite®	diatomaceous earth
conc.	concentrated
mCPBA	3-chloroperoxybenzoic acid
dec.	decomposition
DAST	(diethylamino)sulfur trifluoride
DIAD	diisopropyl azodicarboxylate

DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
DPPF	bis(diphenylphosphino)ferrocene
EDCI·HCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
$KN(SiMe_3)_2$	potassium bis(trimethylsilyl)amide
KO*t*Bu	potassium *tert*-butoxide
$LiAlH_4$	lithium aluminum hydride
$LiBH_4$	lithium borohydride
$LiN(SiMe_3)_2$	lithium bis(trimethylsilyl)amide
MeOH	methanol
NMM	4-methylmorpholine
obs'd	observed
Oxone®	potassium peroxymonosulfate
PCC	pyridinium chlorochromate
Ph_3P	triphenylphosphine
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloro paladium(II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PivCl	trimethylacetyl chloride
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDMSOTf	*tert*-butyldimethylsilyl triflate
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TRIBAL	triisobutylaluminum

Example 1

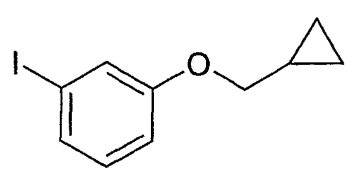
4-(Cyclopropylmethoxy)iodobenzene



A solution of 4-iodophenol (11.0g, 50.0 mmol) in tetrahydrofuran (30 mL + 10 mL rinse) was added to a cooled (0 °C) and stirred suspension of sodium hydride (1.44 g, 60.0 mmol) in tetrahydrofuran (30 mL). The cold bath was removed and the reaction was stirred for 1 h. A solution of (bromomethyl)cyclopropane (16.2 g, 120.0 mmol) in tetrahydrofuran (20 mL) and then HMPA (5 mL) were added successively and the reaction was heated (55 °C) for 18 h. After cooling, the reaction was quenched with cold water (500 mL) and then extracted with ethyl acetate (3x200 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 10% dichloromethane/hexane afforded 12.6 g (92%) of the desired Example **1**. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 2 H), 6.68 (d, 2 H), 3.76 (d, 2 H), 1.20-1.35 (m, 1 H), 0.60-0.70 (m, 2 H), 0.31-0.39 (m, 2 H); mass spectroscopy gave M^+ of 274.0 (calc'd exact mass for $C_{10}H_{11}IO$ = 273.99).

Example 2

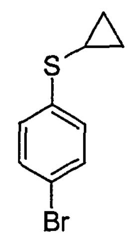
3-(Cyclopropylmethoxy)iodobenzene



3-Iodophenol (11.0g, 50.0 mmol) was converted to 12.4 g (90%) of the desired product using the method described for Example **1**. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.31 (m, 2 H), 6.99 (dd, 1 H), 6.84-6.90 (m, 1 H), 3.77 (d, 2 H), 1.25-1.35 (m, 1 H), 0.60-0.70 (m, 2 H), 0.32-0.39 (m, 2 H); mass spectroscopy gave MH^+ of 275.0 (calc'd exact mass for $C_{10}H_{11}IO$ = 273.99).

Example 3

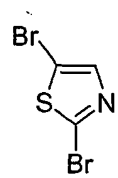
4-Bromo-1-cyclopropylthiobenezene



To a solution of cyclopropylphenyl sulfide (5 g, 34.2 mmol) in 342 mL chloroform, a solution of bromine (1.94 g, 37.6 mmol) in 113 mL chloroform was added dropwise. The reaction mixture was stirred at rt overnight and then quenched with aq. $NaHCO_3$ and sat. $Na_2S_2O_5$. The reaction was extracted with dichloromethane and the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. An oil (6.19 g, 79% yield) was given after distillation. ^{1}H NMR (DMSO, δ = 2.48): 7.45 – 7.49 (m, 2H), 7.25 – 7.30 (m, 2H), 2.22 – 2.28 (m, 1H), 1.04 – 1.10 (m, 2H), and 0.53 - 0.58 (m, 2H). MS [M+H] = 229 (HPLC/MS).

Example 4

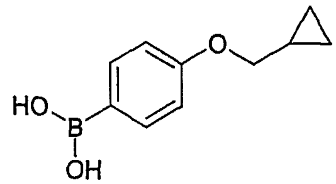
2,5-Dibromo-1,3-thiozole



(Caution: Blast shield recommended). Nitric acid (65%, 11.6 mL) was added slowly to a 0°C solution of commercially available 2-amino-5-bromothiazole monohydrobromide (10 g, 38.4 mmol) in phosphoric acid (85%, 30 mL). The mixture was cooled to –5°C and an aq. solution of sodium nitrite (3.44 g, 50 mmol) was added slowly, while maintaining the bath temperature below 0°C. The mixture was stirred for 2 h. A solution of copper sulfate (8.0 gm) and sodium bromide (10.3 g) in water (30 mL) was added slowly at 0°C and the resulting mixture was stirred for 4 h. The mixture was adjusted to pH 7 and extracted with ether. The combined extracts were dried and concentrated under reduced pressure. Purification of the remaining oil by flash chromatography (silica gel, 10:1 hexane:ethyl acetate) afforded 4.3 g (46%) of Example **4**. Rf = 0.91 (10/1 hexane/ethyl acetate); GCMS (CI) obs'd: 242, 244, 246; calc'd 241.

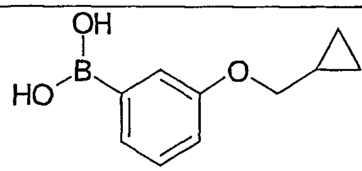
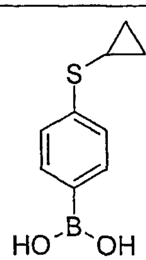
Example 5

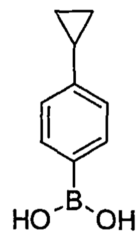
4-(Cyclopropylmethoxy)phenylboronic acid



Butyl lithium (2.5 M in hexane, 14.4 mL, 36 mmol) was added dropwise (5 min) to a cooled (-78 °C) and stirred solution of 4-(cyclopropylmethoxy)iodobenzene **1** (9.00 g, 32.8 mmol) in tetrahydrofuran (100 mL). After 20 min, trimethyl borate (11.3 mL, 10.4 g, 100 mmol) was added dropwise (10 mL). The reaction was stirred for an additional 20 min, and was then allowed to warm to rt. The reaction was quenched with 1 M hydrochloric acid (300 mL) and stirring was continued for 30 min. The product was extracted with diethyl ether (4x100 mL) and then the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in toluene and then concentrated. This operation was repeated (5x) until the distillate was colorless and left 5.67 g (90%) of crude product. This material was used without purification or analysis.

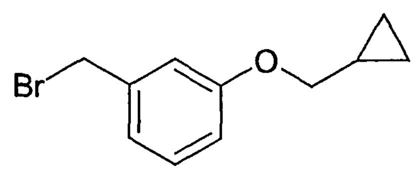
The following compounds were prepared according to the method of Example **5**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
6		93			
7		75			

Ex. No.	Structure	Yield [%]	MS $[M+H^+]$	Rf	mp [°C]
8		85			

Example 9

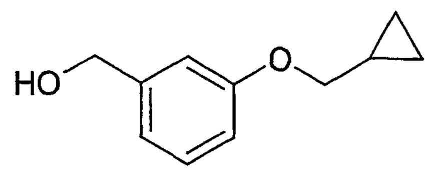
1-(Bromomethyl)-3-(cyclopropylmethoxy)benzene



Pyridine (3.20 mL, 3.13 g, 39.6 mmol) and a solution of dibromophenylphosphorane (13.9 g, 32.9 mmol) in acetonitrile (50 mL) were added successively to a cooled (0 °C) and stirred solution of 1-(hydroxymethyl)-3-(cyclopropylmethoxy)benzene, (Example **10**, 4.40 g, 24.7 mmol) in acetonitrile (100 mL). The mixture was allowed to warm to rt and stirring was continued for 16 h. The reaction was quenched with saturated aqueous sodium thiosulfate (300 mL) and extracted with ethyl acetate (3x200 mL). The combined organic extracts were washed with 1 M hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 20% ethyl acetate/hexane gave 3.80 g (64%) of the Example **9**. The product had: ^1H NMR (300 MHz, acetone-D_6) d 7.22 (t, 1 H), 7.01 (m, 2 H), 6.82-6.88 (m, 1 H), 4.56 (s, 2 H), 3.83 (d, 2 H), 1.16-1.29 (m, 1 H), 0.52-0.62 (m, 2 H), 0.31-0.41 (m, 2 H).

Example 10

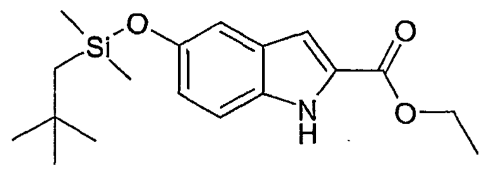
1-(Hydroxymethyl)-3-(cyclopropylmethoxy)benzene



Sodium borohydride (0.75 g, 20 mmol) was added in portions to a stirred solution of 3-(cyclopropylmethoxy)benzaldehyde (Lit: *Chem. Pharm. Bull.* **1975**, *23*, 2878) (3.5g, 20 mmol) in methanol (80 mL). The mixture was stirred for 2 h and then quenched with water (300 mL). The product was extracted with ethyl acetate (3x150 mL) and then the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to leave 3.2 g (89%) of crude product. This material was used in the next reaction without further purification or analysis.

Example 11

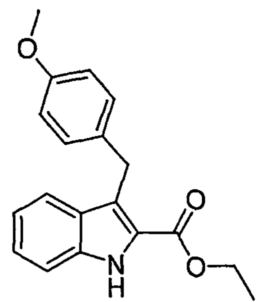
Ethyl 5-(*tert*-butyldimethylsiloxy)-1H-indole-2-carboxylate



Imidazole (2.30 g, 33.2 mmol) and *tert*-butyldimethylsilyl chloride (2.50 g, 16.6 mmol) were added successively to a stirred solution of ethyl 5-hydroxy-1H-indole-2-carboxylate (1.70 g, 8.29 mmol) in dichloromethane (100 mL). The reaction was stirred for 16 h and then diluted with dichloromethane (300 mL). The solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to leave 2.65 g (100%) of Example **11**. The product had: ^{1}H NMR (300 MHz, acetone-D_6) d 10.73-10.88 (br s, 1 H), 7.39 (d, 1 H), 7.11 (d, 1 H), 7.05 (s, 1 H), 6.86 (dd, 1 H), 4.34 (q, 2 H), 1.36 (t, 3 H), 1.09 (s, 9 H), 0.20 (s, 6 H).

Example 12

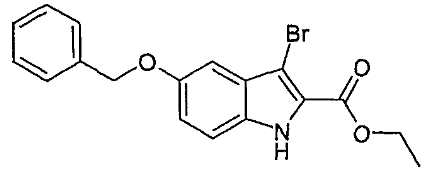
Ethyl 3-[(4-methoxyphenyl)methyl]indole-2-carboxylate



To a solution of ethyl 1-[(4-methoxyphenyl)methyl]indole-2-carboxylate (Example **38**) (950 mg, 3.07 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (1.2 mL). The resulting pink solution was stirred for 18 h at RT. The reaction was quenched with 1.0 N aqueous sodium hydroxide and the organic layer was collected. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous magnesium sulfate, concentrated to an oil, and purified by flash chromatography on silica in 8:1 hexane: ethyl acetate (v/v) to yield 468 mg (49%) of Example **12** of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (s, 1H), 7.64-7.58 (m, 1H), 7.42-7.38 (m, 1H), 7.26-7.14 (m, 3H), 7.02-6.97 (m, 1H), 6.80-6.74 (m, 2H), 4.35 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.65 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); TLF R_f = 0.44 (4:1 Hexane: ethyl acetate (v/v)).

Example 13

Ethyl 5-(benzyloxy)-3-bromo-1H-indole-2-carboxylate

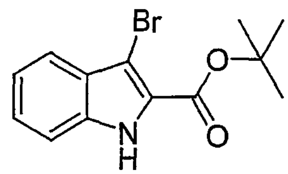


A solution of *N*-bromosuccinimide (7.83 g, 44.0 mmol) in *N,N*-dimethylformamide (30 mL) was added dropwise (40 min) to a cooled (0 °C) and stirred solution of ethyl 5-(benzyloxy)-1H-indole-2-carboxylate (10.0 g, 39.2 mmol) in *N,N*-dimethylformamide (20 mL). The cold bath was removed and stirring was continued for an additional 1.5 h. The reaction was poured over ice water (600 mL) and the resulting precipitate was collected by vacuum filtration. The precipitate was washed with water and

dried to give 12.9 g (98%) of crude product. This material was used in the next reaction without further purification or analysis.

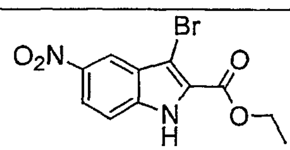
Example 14

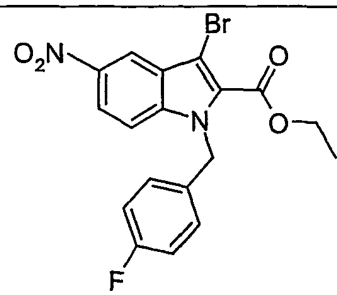
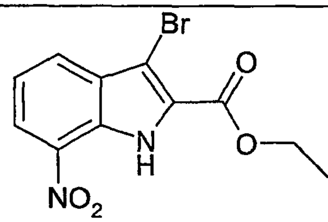
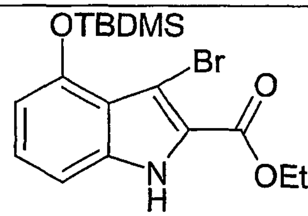
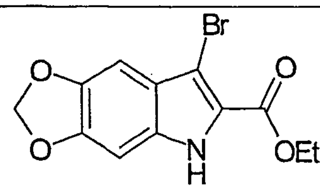
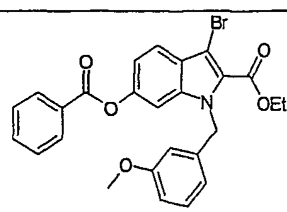
tert-Butyl 3-Bromoindole-2-carboxylate

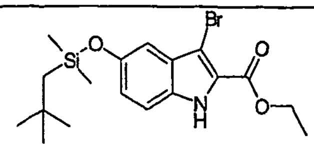


Indole-2-carboxylic acid was converted to 3-bromoindole-2-carboxylic acid using the method described for Example **13**. *N,N*-dimethylformamide di-*tert*-butyl acetal (35 mL) was added dropwise to a stirring mixture of indole-3-bromo-2-carboxylic acid (14.9 g, 62 mmol) suspended in toluene (100 mL). After the addition was complete, the reaction was heated at 90 °C for 8 h. The reaction mixture was then cooled to room temperature and washed with cold water (2x100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield the crude *tert*-butyl 3-bromoindole-2-carboxylate, assume quantitative yield. The crude product was used in the next step without purification.

The following compounds were prepared according to the methods of Examples **13** and **14**:

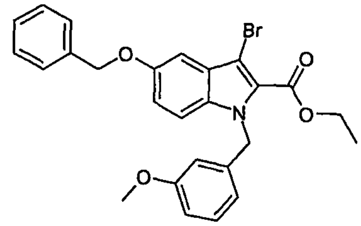
Ex. No.	Structure	Yield [%]	MS $[M+H^+]$	Rf	mp [°C]
15		96		0.58 (Hexane /ethyl acetate 2:1)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
16		58		0.70 (Hexane /ethyl acetate 2:1)	
17		100	312.5		
18		73	398		
19		87		0.4 (Hexane /ethyl acetate 8:2)	
20		92	508.1	0.27 (Hexane /ethyl acetate 8:2)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
21		89			

Example 22

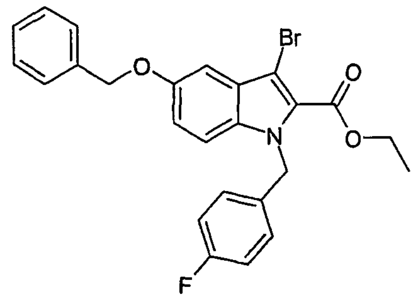
Ethyl 5-(benzyloxy)-3-bromo-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Powdered potassium carbonate (2.79 g, 20.2 mmol) and 3-methoxybenzyl bromide (2.03 g, 10.1 mmol) were added successively to a stirred solution of ethyl 5-(benzyloxy)-3-bromo-1H-indole-2-carboxylate, Lit. WO96/18393 (3.63 g, 9.70 mmol) in *N,N*-dimethylformamide (20 mL). The reaction was stirred for 23 h and then diluted with water (250 mL). The product was extracted with ethyl acetate (3x100 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Recrystalization of the residue using methanol afforded 4.03 g (84%) of the desired product. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05-7.91 (m, 9 H), 6.74 (dd, 1 H), 6.53-6.63 (m, 2 H), 5.37 (s, 2 H), 5.12 (s, 2 H), 4.37 (q, 2 H), 3.71 (s, 3 H), 1.39 (t, 3 H); mass spectroscopy gave MH^+ = 494.1 (calc'd exact mass for $C_{26}H_{24}BrNO_4$ = 493.09).

Example 23

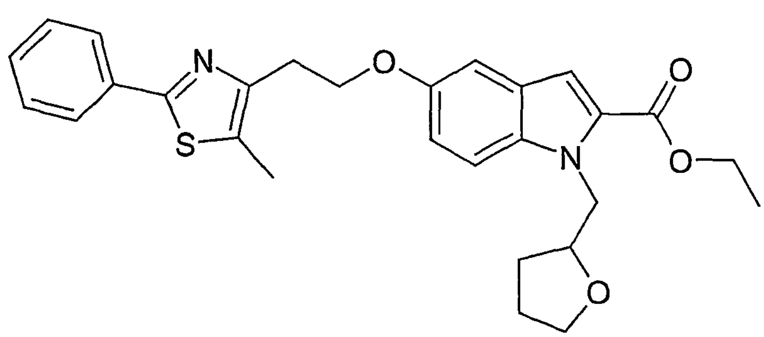
Ethyl 5-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylate



A solution of ethyl 5-(benzyloxy)-3-bromo-1*H*-indole-2-carboxylate, Ref. WO96/18393 (6.77 g, 20.3 mmol, Ref. 96/18393) in *N,N*-dimethylformamide (10 + 5 mL rinse) was added slowly (10 min) to a cooled (0 °C) and stirred suspension of sodium hydride (0.72 g, 30 mmol) in *N,N*-dimethylformamide (30 mL). The reaction was stirred for 1 h and then 4-fluorobenzylbromide (3.7 mL, 5.7 g, 30 mmol) was added. The cold bath was removed and the mixture was stirred for 18 h. The reaction was quenched by pouring over ice water (400 mL) and then the product was extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 50% dichloromethane/hexane gave 6.80 g (75%) of the desired product containing trace impurities. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84-7.53 (m, 12 H), 5.72 (s, 2 H), 5.13 (s, 2 H), 4.38 (q, 2 H), 1.40 (t, 3 H).

Example 24

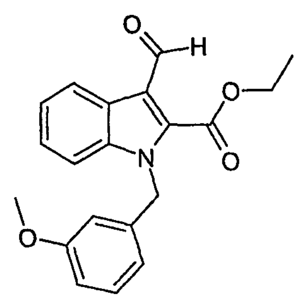
Ethyl 5-[2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]-1-(tetrahydro-2-furanylmethyl)-1*H*-indole-2-carboxylate



A solution of ethyl 5-[2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]-1*H*-indole-2-carboxylate **220** (40.7 mg, 0.100 mmol) in *N,N*-dimethylformamide (0.9 mL) was added to a stirred mixture of cesium carbonate (325 mg, 1.00 mmol) and 2-(bromomethyl)tetrahydrofuran (19.8 mg, 0.120 mmol) in *N,N*-dimethylformamide (2.4 mL). The reaction was stirred for 16 h and then the mixture was filtered though a plug (500 mg) of silica gel using ethyl acetate to rinse. The filtrate was concentrated *in vacuo* and then reverse phase preparative HPLC chromatography gave 19.8 mg of product (retention time = 2.4 min.). This material was taken to the next reaction without further purification or analysis.

Example 25

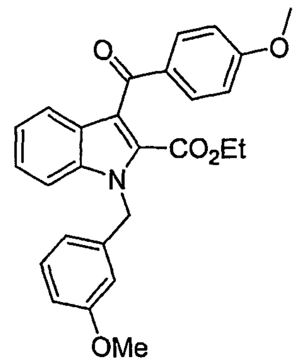
Ethyl 3-formyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Sodium hydride (60% dispersion in mineral oil, 2.40 g, 60.0 mmol) was cooled to 0 °C, and anhydrous methyl sulfoxide (75.0 mL, 1.06 mol) was added. The mixture was stirred at 0 °C for 15 minutes before a solution of ethyl 3-formyl-1H-indole-2-carboxylate (10.9 g, 50.2 mmol, Lit. *J. Heterocyclic Chem.* **1997**, *34*, 1431.) in 75 mL of methyl sulfoxide was added over a 20 minute period. The resulting solution was warmed to room temperature and stirred for 1 hour. 3-Methoxybenzylbromide (9.8 mL, 70.0 mmol) was added, and the solution was heated at 60 °C for 16 hours. The solution was cooled and poured into water (500 mL). The aqueous solution was extracted with ethyl acetate (3x), and the combined organic extracts were washed with 1 N hydrochloric acid (2x), water, and brine. The solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Trituration of the residue with 33% hexane/Et_2O provided the title compound as a solid (13.8 g, 81%). The product had: ^{1}H NMR (300 MHz, acetone-d_6) δ 10.61 (s, 1 H), 8.43 (d, 1 H), 7.61 (d, 1 H), 7.30-7.45 (m, 2 H), 7.19 (dd, 1 H), 6.80 (dd, 1 H), 6.63-6.74 (m, 2 H), 5.88 (s, 2 H), 4.48 (dq, 2 H), 3.70 (s, 3 H), 1.37 (t, 3 H); mass spectroscopy gave MH^+ = 338.1 (calc'd exact mass for $C_{20}H_{19}NO_4$ = 337.13).

Example 26

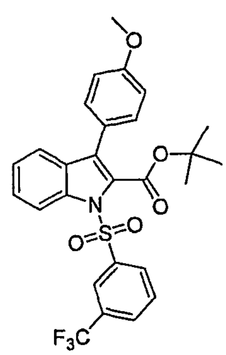
Ethyl 3-(4-methoxybenzoyl)-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Indole **203** (244 mg, 0.76 mmol) was added to a suspension of sodium hydride (36 mg, 0.91 mmol) in *N,N*-dimethylformamide (3 mL). After 10 min., sodium iodide (20 mg, 0.133 mmol) and 3-methoxybenzyl chloride (0.13 mL, 0.91 mmol) was added and the resulting mixture was stirred at rt. for ~15 h. Purification (silica gel chromatography 25:75 ethyl acetate:hexane) afforded 236 mg (70%) of Example **26**. Rf = 0.33 (75/25 hexane/ethyl acetate); LRMS (+esi) obs'd: 444.1; calc'd 443.17.

Example 27

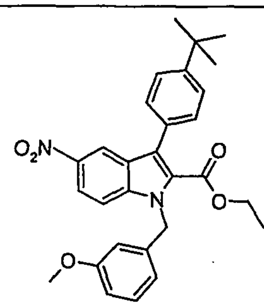
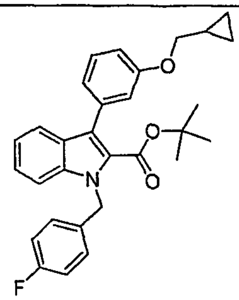
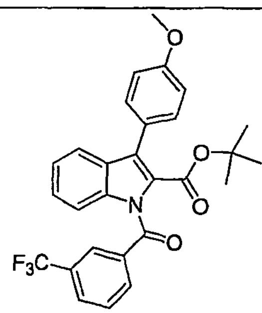
tert-Butyl 3-(4-Methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylate

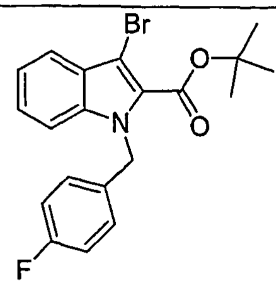
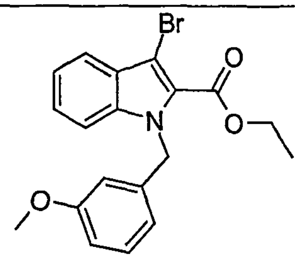
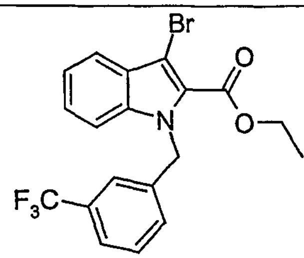
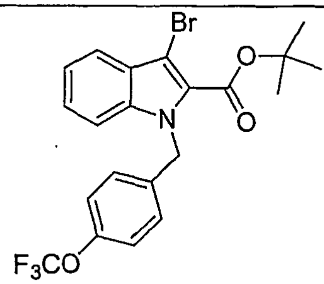
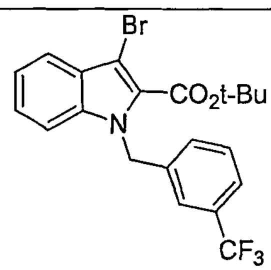


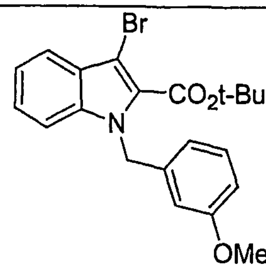
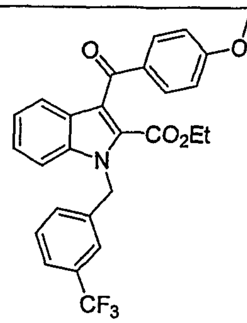
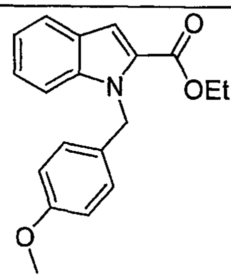
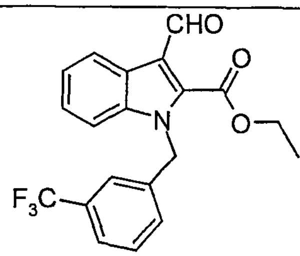
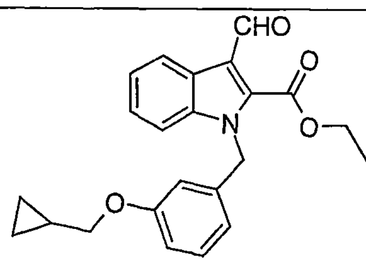
To a stirring solution of *tert*-butyl-3-(4-methoxyphenyl)indole-2-carboxylate (Example **105**, 75 mg, 0.23 mmol) in tetrahydrofuran (0.4 mL) was added potassium *tert*-butoxide (1 M in tetrahydrofuran, 0.4 mL) in one aliquot. After 10 minutes chloro[3-(trifluoromethyl)phenyl]sulfone (113 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with ethyl acetate (4 mL) and quenched with water (2 mL). The organic phase was extracted with ethyl acetate (3 x 4mL). The combined organic layers were dried over anhydrous

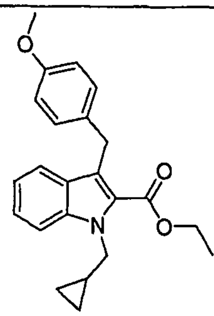
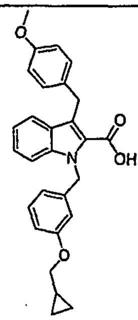
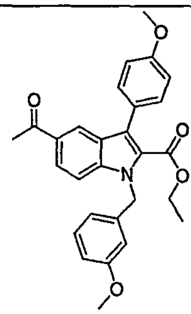
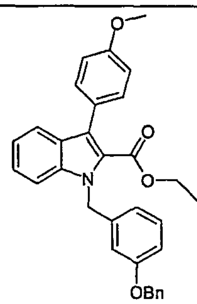
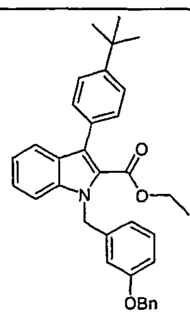
magnesium sulfate and concentrated under reduced pressure. The crude product was filtered through a plug of silica gel (30% ethyl acetate/hexane) to provide *tert*-butyl 3-(4-methoxyphenyl)-1-{[3-(trifluoromethyl)phenyl]sulfonyl}indole-2-carboxylate (45 mg, 37%), which was used in the next step without further purification.

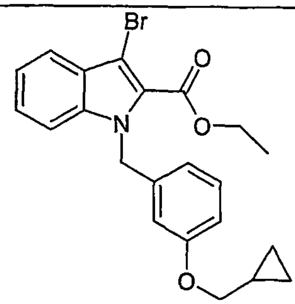
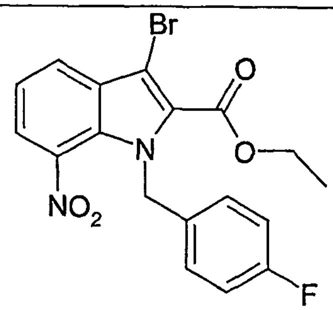
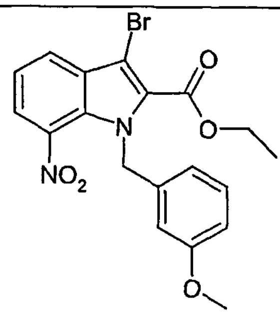
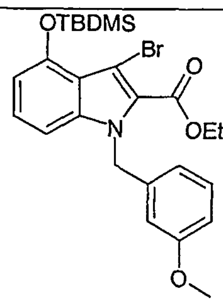
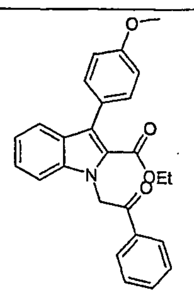
The following compounds were prepared according to the methods of Examples **22 - 27**:

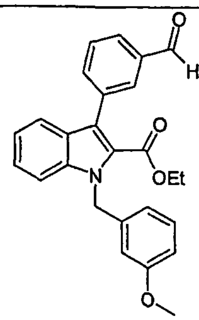
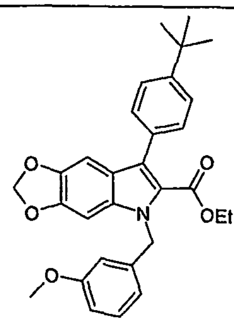
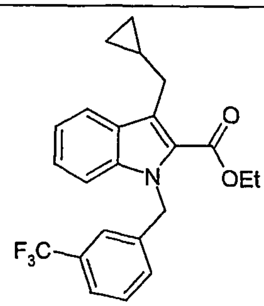
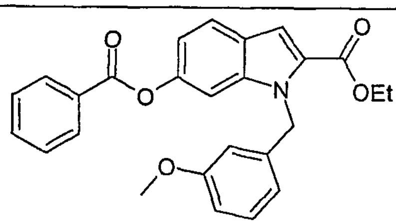
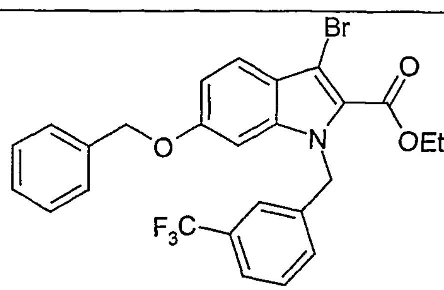
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
28		50			
29		44			
30		27			

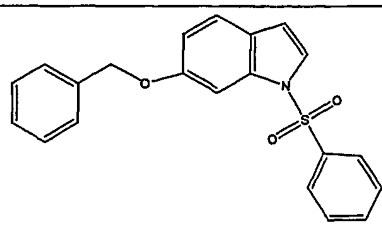
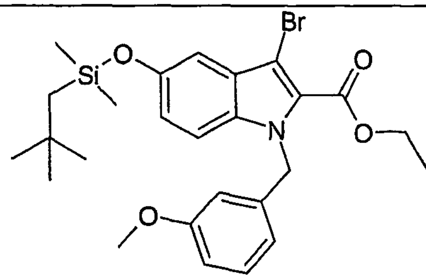
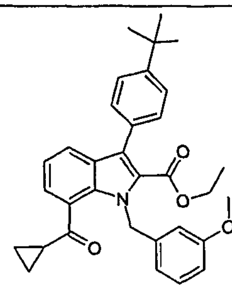
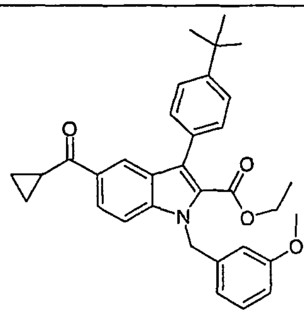
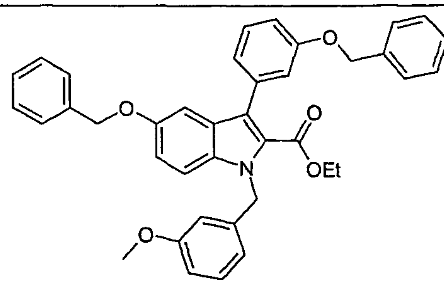
Ex. No.	Structure	Yield [%]	MS [M+H⁺]	Rf	mp [°C]
31		54			
32		73	390		
33		88	426	0.50 (hexane/ ethyl acetate 9:1)	
34		39			
35		crude			

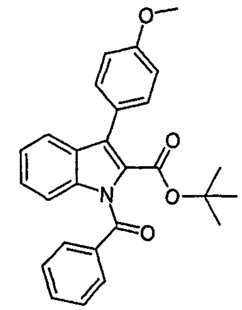
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
36		98	360.0	0.59 (Hexane/ ethyl acetate 7:1)	
37		96	482.1	0.38 (Hexane/ ethyl acetate 3:1)	
38		58	562.2	0.72 (Hexane/ ethyl acetate 4:1)	
40		80	376.1	0.31 (Hexane/ ethyl acetate 2:1)	
41		crude			

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
42		77		0.56 (Hexane/ ethyl acetate 4:1)	
43		76	598.2	0.48 (Hexane/ ethyl acetate 4:1)	
44		64		0.39 (Hexane/ ethyl acetate 4:1)	
45		100 crude			
46		100 crude			

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
47		51	428		
48		78	421		
49		58	433		
50		40		0.65 (Hexane/ ethyl acetate 3:1)	
51		100 crude			

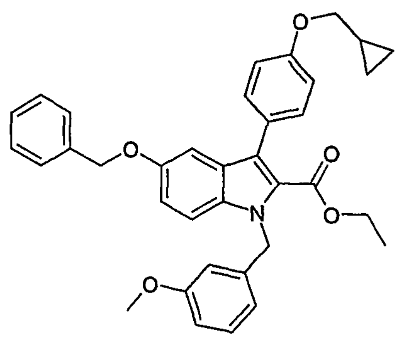
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
52		32			
53		55		0.53 (Hexane/ ethyl acetate 4:1)	
54		72	416.4	0.58 (Hexane/ ethyl acetate 9:1)	
55		34	432.4	0.60 (Hexane/ ethyl acetate 4:1)	
56		90	454.3	0.75 (Hexane/ ethyl acetate 7:3)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
57		88		0.55 (Hexane/ ethyl acetate 4:1)	
58		87			
59		71			
60		40			
227		75	598.2		

Ex. No.	Structure	Yield [%]	MS [$M+H^+$]	Rf	mp [°C]
228		27 crude			

Example 61

Ethyl 5-(benzyloxy)-3-[4-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylate

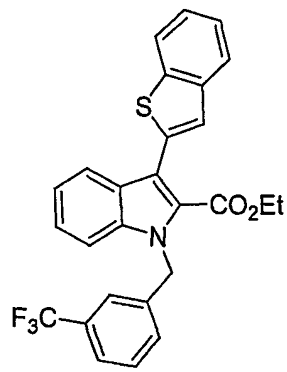


Example **5** (2.30 g, 12.0 mmol) and 2 M aqueous sodium carbonate (20 mL) were added to a stirred solution of ethyl 5-(benzyloxy)-3-bromo-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (4.03 g, 8.15 mmol) in EtOH (30 mL) and toluene (30 mL). Argon was bubbled through the mixture for 15 min and then tetrakis(triphenylphosphine)palladium(0) (1.15 g, 1.00 mmol) was added. The reaction was heated (85 °C) for 16 h and then cooled. The mixture was diluted with 1 M hydrochloric acid (200 mL) and then extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 60% dichloromethane/hexane gave 3.41 g (75%) of Example **61**. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95-7.48 (m, 13 H), 6.65-6.77 (m, 3 H), 5.76 (m, 2 H), 5.01 (s, 2 H), 4.13 (q, 2 H), 3.90 (d, 2 H), 3.74 (s, 3 H), 1.30-1.41 (s, 1 H), 1.05

(t, 3 H), 0.65-0.75 (m, 2 H), 0.38-0.45 (m, 2 H); mass spectroscopy gave MH^+ = 562.2 (calc'd exact mass for $C_{36}H_{35}NO_5$ = 561.25).

Example 62

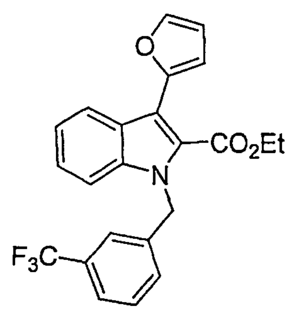
Ethyl 3-(benzothiozole)-1-(3-trifluoromethylbenzyl)-indole-2-carboxylate



A mixture of Example **33** (300 mg, 0.70 mmol), benzothiophene-2-boronic acid (195 mg, 1.1 mmol), 2N Na_2CO_3 (0.7 mL) and *N,N*-dimethylformamide (7 mL) was flushed with argon. $Pd(OAc)_2$ (16 mg, 0.07 mmol) and P(o-tolyl)$_3$ (43 mg, 0.14 mmol) were added and the mixture was heated at 100°C for ~15 h. The mixture was cooled and filtered through a short column of silica gel and sodium bicarbonate (elution with ethyl acetate). The filtrate was concentrated and the remaining oil was purified by flash chromatography (silica gel, 7:1 hexane:ethyl acetate) to afford 178 mg (53%) of Example **62** as a white solid. Rf = 0.51 (7/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 480.0; calc'd 479.1.

Example 63

Ethyl 3-(2-furyl)-1-(3-trifluoromethylbenzyl)-indole-2-carboxylate

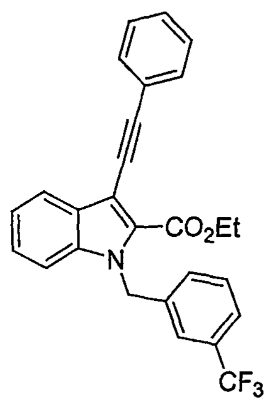


A mixture of Example **33** (300 mg, 0.70 mmol), 2-(tributylstannyl)furan (0.22 mL, 0.7 mmol), lithium chloride (30 mg, 0.7 mmol) and *N,N*-dimethylformamide (7 mL) was

flushed with argon. Tetrakis(triphenylphosphine) palladium (80 mg, 0.07 mmol) was added and the mixture was heated at 100°C for ~15 h. The mixture was cooled and filtered through a short column of silica gel (elution with ethyl acetate). The filtrate was washed with water and brine, concentrated and the remaining oil was purified by flash chromatography (silica gel, 7:1 hexane:ethyl acetate) to afford 160 mg (55%) of Example **63** as a white solid. Rf = 0.45 (7/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 414.1; calc'd 413.1.

Example 64

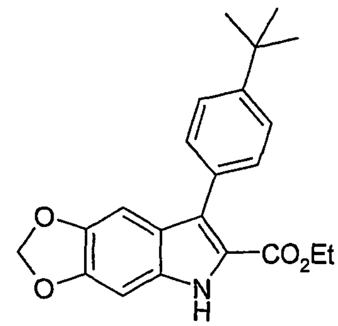
Ethyl 3-(2-phenylethynyl)-1-(3-trifluoromethylbenzyl)-1H-indole-2-carboxylate



A suspension/solution of Example **33** (500 mg, 1.17 mmol), phenyl acetylene (600 mg, 5.86mmol), triethyl amine (5.5 mL) in dry *N,N*-dimethylformamide (12 mL) was flushed with argon. Copper iodide (73 mg, 0.38 mmol) and Pd(dppf)$_2$Cl$_2$-dichloromethane (96 mg, 0.12 mmol) was added and again the system was flushed with Ar. The mixture was then heated at 79°C for 70 min. The suspension was filtered through Celite® (elution with ether) and the filtrate was washed water (3x 20 mL) and brine (20 mL). The ether layer was again filtered through silica to remove precipitates (elution with ether). The filtrate was concentrated and the remaining oil was purified by radial chromatography (4 mm silica gel plate, 95/5 hexane/ethyl acetate) to afford 23 mg (4%) of Example **64** as a brown solid. Rf = 0.23 (95/5 hexane/ethyl acetate).

Example 65

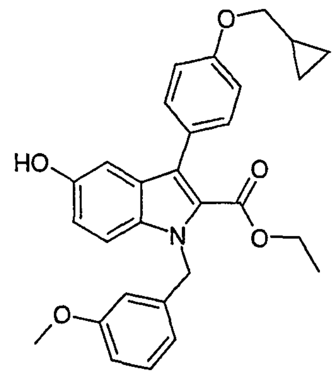
Ethyl 7-(4-tert-butylphenyl)-5H-[1,3]dioxolo[4,5]-findole-6-carboxylate



To a dry 100 mL round bottom flask and stir bar, purged with argon gas, was charged with 0.14g of $Pd_2(dba)_3$ and 0.14g trifurylphosphine followed by addition of 5 ml of toluene. The contents were stirred until homogeneous at which time a of ethyl 7-bromo-5H-[1,3]dioxolo[4,5-f]-indole-6-carboxylate (Example **19**, 1.92 g, 6.13 mmol) in toluene (5 mL) was added to the catalyst solution via cannula. After approximately 10-15 minutes of stirring a 10 mL ethanol solution of 4-tert-butyl-phenyl boronic acid (1.64g, 9.2 mmol) to a stirring solution via cannula. This was followed by addition of 15mL of 2M sodium carbonate dropwise to the pot. The contents were heated to reflux overnight. The reaction was then quenched with 3 N hydrochloric acid and extracted with 3 times with 30 mL of ethyl acetate. The organic layer was then dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude material was purified via column chromatography yielding 1.24 g (55%) of a white solid (Rf- 0.38 20% ethyl acetate/hexane). The product had: ^1H NMR (300 MHz, acetone-D_6) 7.46 Hz (d, 1 H), 7.02 Hz (d, 1H) 6.97 Hz (d, 2H), 6.87 Hz (d, 2H), 5.99 Hz (d, 2H), 4.18 Hz (q, 2H), 1.35 Hz (s, 9H), 1.32 Hz (t, 3H).

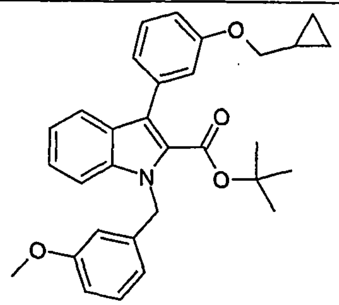
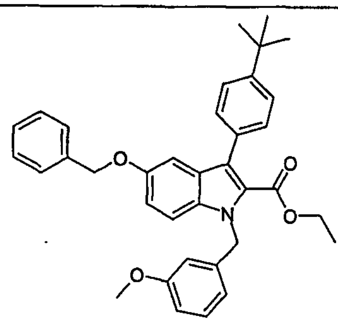
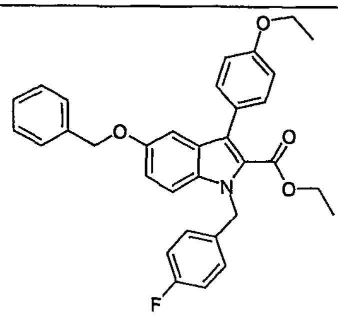
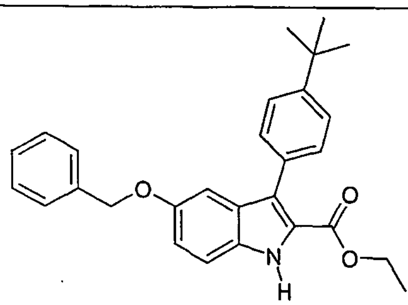
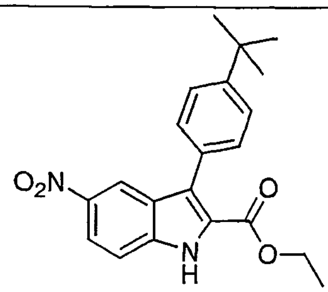
Example 66

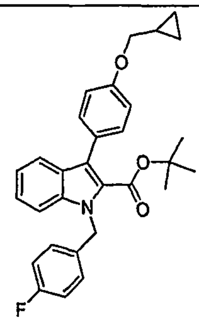
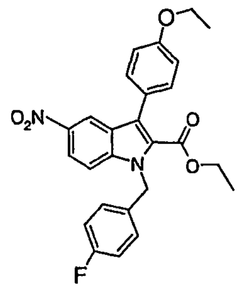
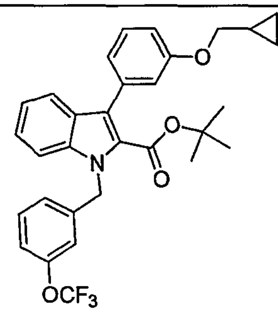
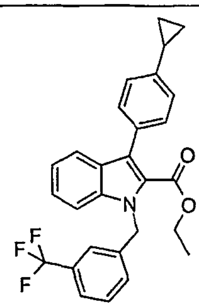
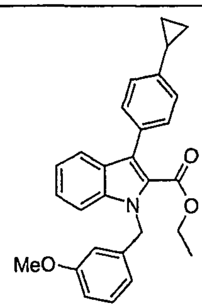
Ethyl 3-[4-(cyclopropylmethoxy)phenyl]-5-hydroxy-1-(3-methoxybenzyl)-1H-indole-2-carboxylate

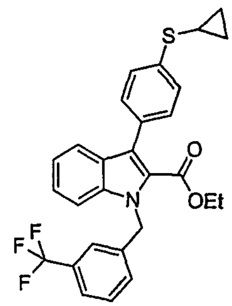
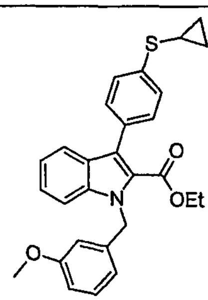
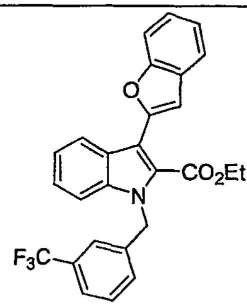
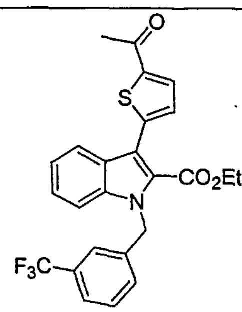
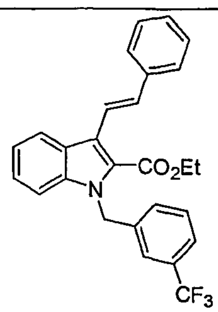


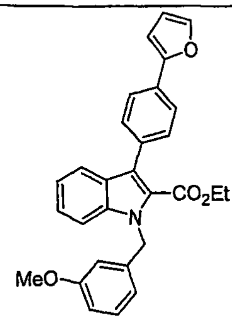
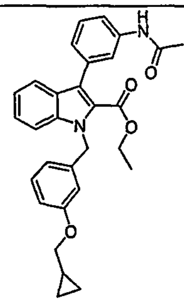
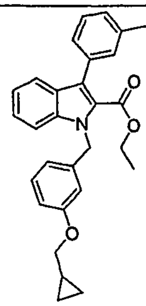
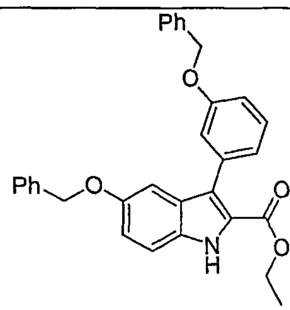
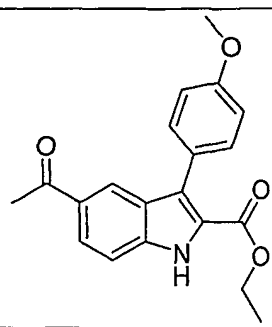
1-Bromo-4-cyclopropylmethoxy)benzene (2.30 g, 12.0 mmol) and 2 M aqueous sodium carbonate (20 mL) were added to a stirred solution of ethyl 5-(TBDMSO)-3-bromo-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **58**, 4.03 g, 8.15 mmol) in ethanol (30 mL) and toluene (30 mL). Argon was bubbled through the mixture for 15 min and then tetrakis(triphenylphosphine)palladium(0) (1.15 g, 1.00 mmol) was added. The reaction was stirred with heating (85 °C) for 16 h and then cooled. The mixture was diluted with 1 M hydrochloric acid (200 mL) and then extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (100 mL) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 20 mL, 20 mmol) was added. The reaction was stirred for 1 h and then diluted with ethyl acetate (300 mL). The solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 20% ethyl acetate/hexane afforded 1.10 g (65%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.85 (s, 1 H), 7.28-7.37 (m, 3 H), 7.12 (dd, 1 H), 6.84-7.00 (m, 4 H), 6.61-6.74 (m, 3 H), 5.73 (s, 2 H), 4.09 (q, 2 H), 3.86 (d, 2 H), 3.67 (s, 3 H), 1.20-1.32 (m, 1 H), 0.84 (t, 3 H), 0.52-0.63 (m, 2 H), 0.31-0.41 (m, 2 H).

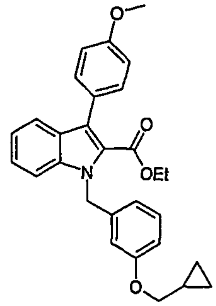
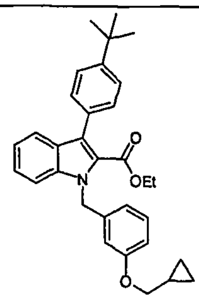
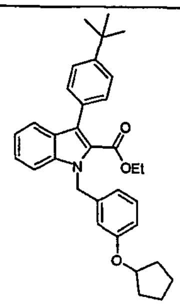
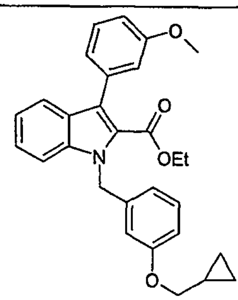
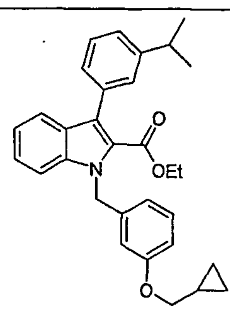
The following compounds were prepared according to the methods of Example **61 - 66:**

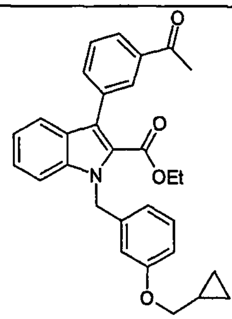
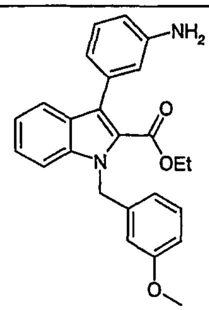
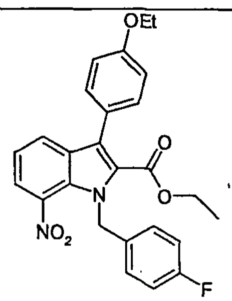
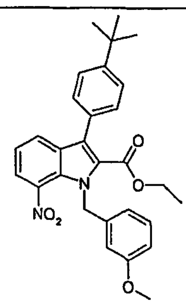
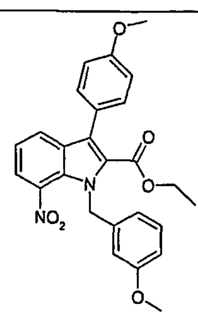
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
67		33	484.3		
68		86	548.2	0.82 (Hexane/ ethyl acetate 2:1)	
69		68	428.2	0.8 (Hexane/ ethyl acetate 2:1)	
70		68	428.2	0.80 (Hexane/ ethyl acetate 2:1)	
71		66		0.62 (Hexane/ ethyl acetate 2:1)	

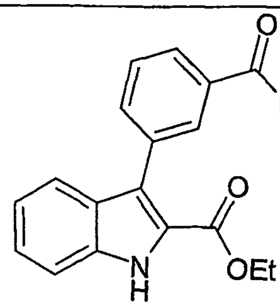
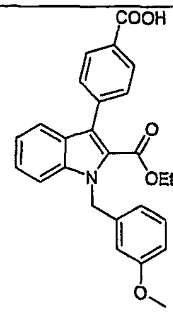
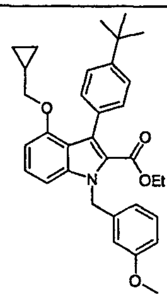
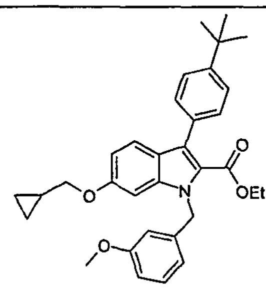
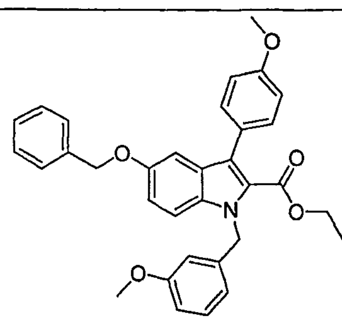
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
72		55			
73		73		0.71 (Hexane/ ethyl acetate 2:1)	
74		43			
75		50	464		
76		56	426		

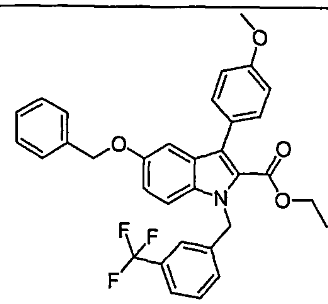
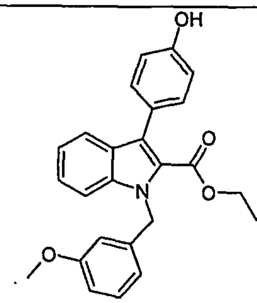
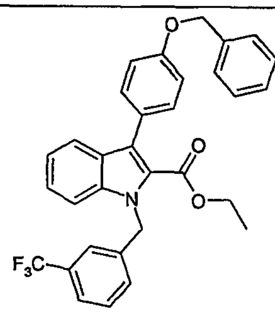
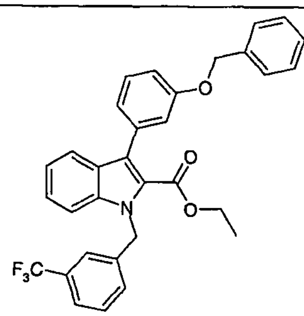
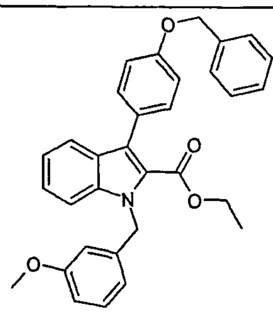
Ex. No.	Structure	Yield [%]	MS [M+H⁺]	Rf	mp [°C]
77		71	496		
78		67	458		
79		25		0.53 (Hexane/ ethyl acetate 7:1)	
80		62	472.2	0.3 (Hexane/ ethyl acetate 7:1)	
81		crude	450.1	0.26 (Hexane/ ethyl acetate 95:5)	

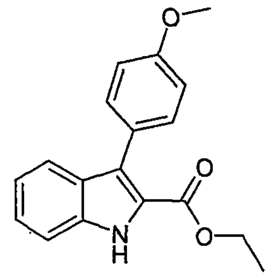
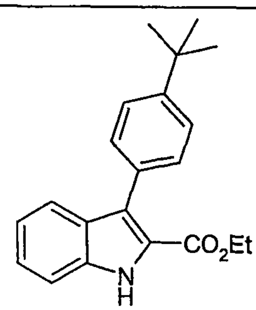
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
82		88	452.2	0.49 (hexane/ ether 8:2)	
83		61	483.1	0.31 (Hexane/ ethyl acetate 1:1)	
84		crude	440.2	0.45 (Hexane/ ethyl acetate 9:1)	
85		67	478.1	0.32 (Hexane/ ethyl acetate 4:1)	
86		45		0.24 (Hexane/ ethyl acetate 4:1)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
87		74			
88		68			
89		80			
90		100		0.56 (Hexane/ ethyl acetate 4:1)	
91		100		0.71 (Hexane/ ethyl acetate 4:1)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
92		57	468	0.50 (Hexane/ ethyl acetate 3:1)	
93		62		0.50 (Hexane/ ethyl acetate 2:1)	
94		75	463		
95		79			
96		100	461		

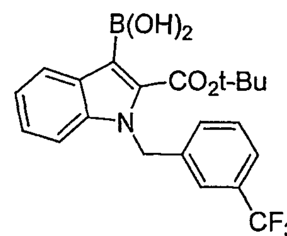
Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
97		73	294 (M$^+$) GC-MS		
98		64			
99		50			
100		27	512.7	0.7 (Hexane/ ethyl acetate 4:1)	
101		69	522.8		

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
102		74	560.1	0.36 (Hexane/ ethyl acetate 6:1)	
121		77	402		
225		77			
226		72			
103		86	492		

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
105		53			
224		93		0.50 (Hexane/ ethyl acetate 4:1)	

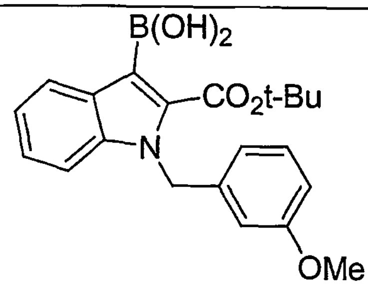
Example 106

2-*tert*-Butoxycarbonyl) 1-[3-(trifluoromethyl)benzyl]-indole-3-yl boronic acid



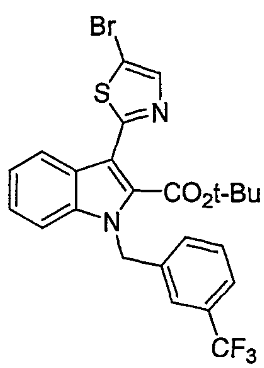
A solution of butyllithium in hexane (7.10 mL, 1.6 M) was added to a –78°C solution of Example **35** (4.95 gm, 10.9 mmol) in tetrahydrofuran (30 mL). After 5 min., trimethyl borate (3.72 mL, 32.7 mmol) was added and the mixture was allowed to warm to rt. over 2 h. 2N hydrochloric acid (30 mL) was added and the mixture was vigorously stirred for 30 min. Ethyl acetate was added and the layers were separated. The organic layer was dried and concentrated. Trituration of the remaining oil with ether followed by drying under reduced pressure afforded 2.3 g (50%) of Example **106** as a white solid. Rf = 0.29 (4/1 hexane/ethyl acetate).

The following compounds were prepared according to the methods of Example **106**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
108		44		0.28 (Hexane/ethyl acetate 4:1)	

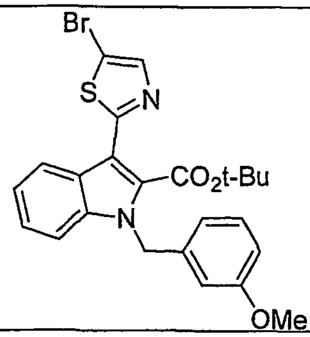
Example 109

***tert*-Butyl 3-(5-bromo-1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylate**



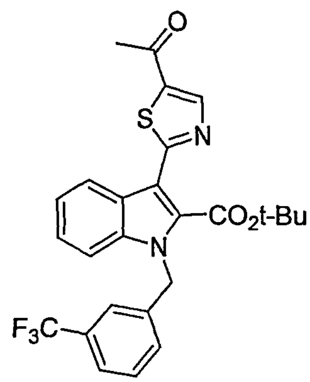
To a solution of Example **106** (150 mg, 0.36 mmol) and Example **4** (68 mg, 0.28 mmol) in toluene (0.7 mL) and ethanol (0.7 mL) was added aq. Na_2CO_3 (0.36 mL, 2N). The reaction vessel was flushed with Ar for 10 min. Tetrakis(triphenylphosphine)-palladium (34 mg, 0.029 mmol) was added and the mixture was heated at 85°C until the disappearance of the boronic acid. The mixture was cooled and filtered. The filtrate was concentrated and the remaining oil was purified by flash chromatography (silica gel, 7:1 hexane:ethyl acetate) to afford 100 mg (66%) of Example **109** as a yellow solid. Rf = 0.61 (7/1 hexane/ethyl acetate); LRMS (+esi) obs'd: 536.8; calc'd 536.0.

The following compounds were prepared according to the method of Example **109**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
110		43	498.9	0.72 (Hexane/ethyl acetate 4:1)	

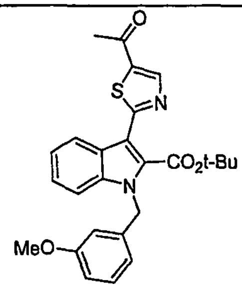
Example 111

***tert*-Butyl 3-(5-acetyl-1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)benzyl]-indole-2-carboxylate**



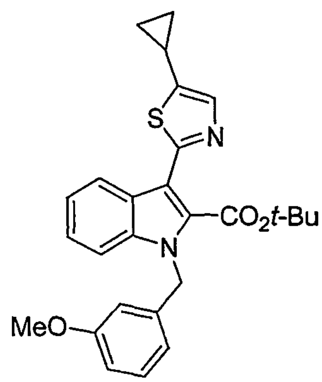
A mixture of Example **108** (300 mg, 0.56 mmol), $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) and lithium chloride (80 mg, 1.68 mmol) in tetrahydrofuran (2 mL) and toluene (2 mL) was flushed with argon. 1-Ethoxyvinyl tri-*n*-butylstannane (224 mg, 0.62 mmol) was added and the mixture was heated at 90 °C for 4 h. A second portion of stannane (107 mg, 0.30 mmol) was added and heating was continued for 1 h. The mixture was cooled to rt. and 10% hydrochloric acid (2 mL) was added. The mixture was stirred for 1 h. The mixture was washed with water, dried and concentrated. The oil thus obtained was purified by flash chromatography (silica gel, 5:1 hexane:ethyl acetate) to afford 280 mg of slightly impure Example **111** which was used without further purification. LRMS (+esi) obs'd: 500.9; calc'd 500.1.

The following compounds were prepared according to the method of Example **111**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
111A		crude	463.0	0.32 (Hexane/ethyl acetate 5:1)	

Example 112

tert-Butyl 3-(5-cyclopropyl-1,3-thiazol-2-yl)-1-(3-methoxybenzyl)-indole-2-carboxylate



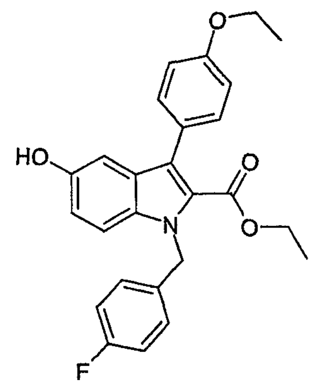
Cyclopropyl boronic acid: A solution of *t*-butyllithium in hexane (17.0 mL, 25.4 mmol) was added to a –78°C solution of cyclopropyl bromide (1.51 gm, 12.4 mmol) in dry tetrahydrofuran (20 mL). After stirring for 15 min., trimethoxy borate (1.23 gm, 11.8 mmol) was added and the resulting mixture was warmed to rt. over 1h. 2N HCl (15 mL) was added and the aq. phase was extracted with ethyl acetate. The extracts were dried over anhydrous sodium sulfate and concentrated to give the cyclopropyl boronic which was used in the coupling step without further purification.

A mixture of cyclopropyl boronic acid (75 mg, 0.84 mmol), Example **110** (200 mg, 0.42 mmol), Na_2CO_3 (2N, 0.9 mL), and *N,N*-dimethylformamide (3.5 mL) was flushed with argon. Palladium(II) acetate (18 mg, 0.08 mmol) and $P(o\text{-tolyl})_3$ (50 mg, 0.16 mmol) were added and the mixture was heated at 100°C for 1 h. The mixture was cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried

over anhydrous sodium sulfate and concentrated. Purification of the remaining oil by flash chromatography gave slightly impure Example **112** which was used without further purification. LRMS (+esi) obs'd: 461.0; calc'd 460.2.

Example 113

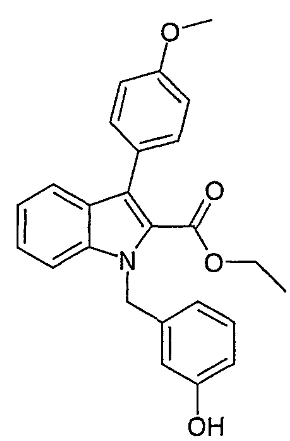
Ethyl 3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-5-hydroxy-1*H*-indole-2-carboxylate



A solution of ethyl 5-(benzyloxy)-3-(4-ethoxyphenyl)-1-(4-fluorobenzyl)-1*H*-indole-2-carboxylate (Example **69**, 4.7 g, 9.0 mmol) in ethyl acetate (15 mL) was added to a suspension of 10% palladium on charcoal (2.0 g) in ethyl acetate (10 mL). The mixture was placed under an atmosphere of hydrogen (1 atm) and stirred for 16 h. The reaction was filtered through a pad of Celite using ethyl acetate to rinse. Evaporation of the filtrate left 3.5 g (90%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.98 (s, 1 H), 6.89-7.42 (m, 11 H), 5.81 (s, 2 H), 4.03-4.19 (m, 4 H), 1.41 (t, 3 H), 1.04 (t, 3 H).

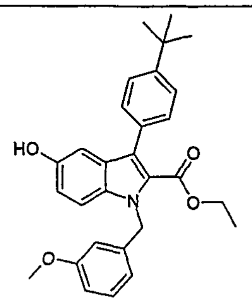
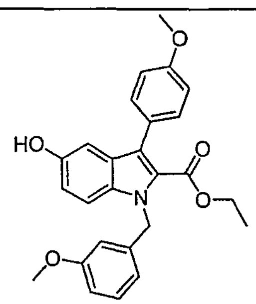
Example 114

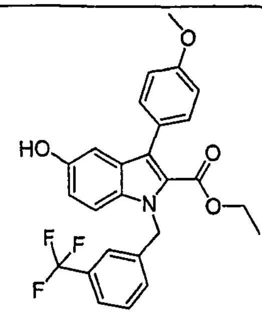
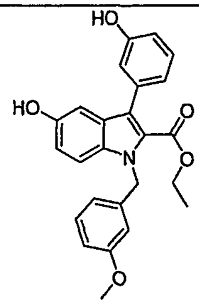
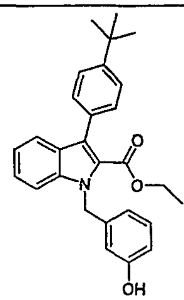
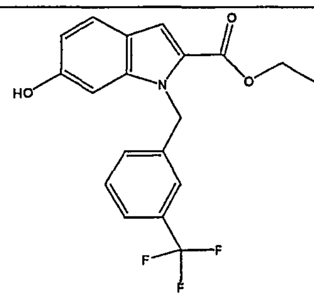
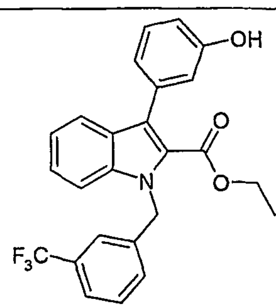
Ethyl 1-[(3-hydroxyphenyl)methyl]-3-(4-methoxyphenyl)indole-2-carboxylate

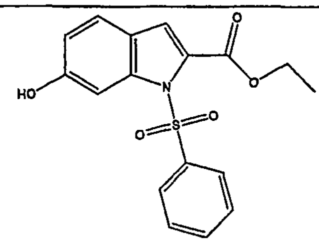


To a Parr shaker bottle purged with Argon was added palladium on carbon (Degussa type) (500 mg), ethyl acetate (10 mL), ethyl 3-(4-methoxyphenyl)-1-{[3-(phenylmethoxy)phenyl]methyl}indole-2-carboxylate (Example **45**, 5 g crude material, 7.0 mmol, in 120 mL methanol and 40 mL ethyl acetate). The mixture was hydrogenated at 55 psi for 48 h. The mixture was then filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified with silica gel flash chromatography using hexane/ethyl acetate (3/1 to 2/1) to give ethyl 1-[(3-hydroxyphenyl)methyl]-3-(4-methoxyphenyl)indole-2-carboxylate as a light yellow oil (2.5 g, 89%): MS (M^+) calcd for $C_{25}H_{23}NO_4$ 401.1, found 401.0; ^1H NMR ($CDCl_3$) δ 7.60 (dd, J = 8.1 Hz, 1H), 7.30-7.45 (m, 4H), 7.13-7.21 (m, 2H), 6.98 (d, J = 8.1 Hz, 2H), 6.64-6.78 (m, 2H), 6.52 (s, 1H), 5.77 (s, 2H), 4.14 (q, J = 7.0 Hz, 2H), 1.04 (t, J = 7.0 Hz, 3H).

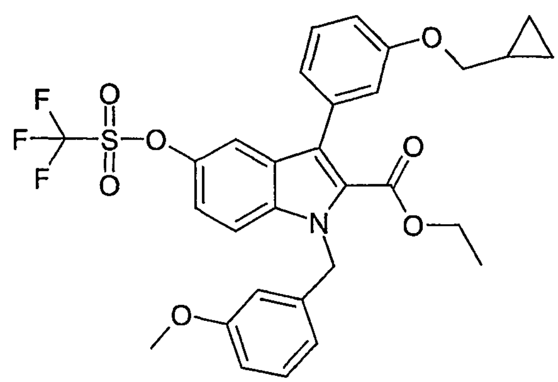
The following compounds were prepared according to the method of Example **114**:

Ex. No.	**Structure**	**Yield [%]**	**MS [M+H$^+$]**	**Rf**	**mp [°C]**
115		93	458.2	0.67 (Hexane/ethyl acetate 2:1)	
116		97	432.1	0.35 (Hexane/ethyl acetate 2:1)	

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
117		92	470.1	0.41 (Hexane/ethyl acetate 2:1)	
118		100	417.2	0.22 (Hexane/ethyl acetate 2:1)	
119		56			
120		63			
122		86			

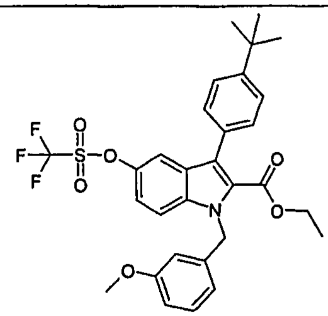
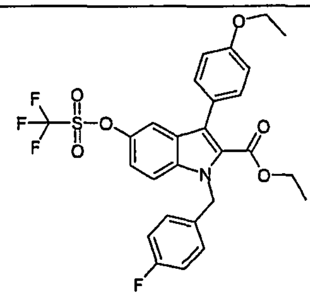
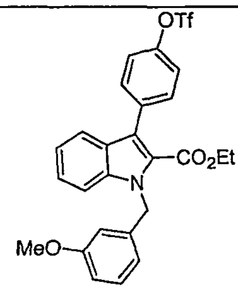
Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
123		96		0.19 (Hexane/ethyl acetate 4:1)	

Example 124
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-{[(trifluoromethyl) sulfonyl]oxy}-1*H*-indole-2-carboxylate



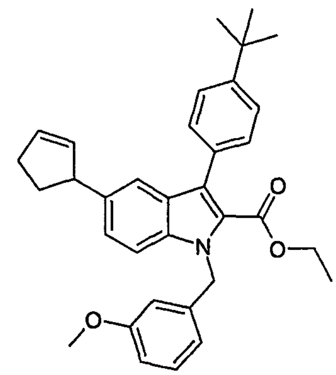
Triflic anhydride (0.84 mL, 1.4 g, 5.0 mmol) and dimethylaminopyridine (25 mg, 0.20 mmol) were added to a cooled (0 °C) and stirred solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-5-hydroxy-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **66**, 1.00 g, 2.12 mmol) in dichloromethane (10 mL) and pyridine (2 mL). The reaction was warmed to rt and then stirred an additional 2 h. The solution was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 15% ethyl acetate/hexane afforded 1.14 g (89%) of desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.73 (d, 1 H), 7.54 (d, 1 H), 7.35-7.42 (m, 3 H), 7.20 (dd, 1 H), 7.00-7.07 (m, 2 H), 6.68-6.83 (m, 3 H), 5.88 (s, 2 H), 4.16 (q, 2 H), 3.91 (d, 2 H), 3.72 (s, 3 H), 1.25-1.35 (m, 1 H), 10.5 (t, 3 H), 0.55-0.65 (m, 2 H), 0.32-0.42 (m, 2 H); mass spectroscopy gave M^+ = 603.1 (exact mass calc'd for $C_{20}H_{28}F_3NO_7S$ = 603.15).

The following compounds were prepared according to the method of Example **124**:

Ex. No.	Structure	Yield [%]	MS [M+H+]	Rf	mp [°C]
125		96			
126		52			
127		48	533.9		

Example 128

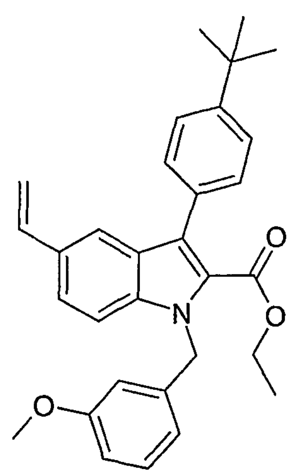
Ethyl 3-(4-*tert*-butylphenyl)-5-(2-cyclopenten-1-yl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Cyclopentene (0.44 mL, 341 mg, 5.0 mmol), palladium acetate (22 mg, 0.10 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol) and potassium acetate (295 mg, 1.0 mmol) were added to a stirred solution of ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1*H*-indole-2-carboxylate (Example **125**, 570 mg, 1.0 mmol) in *N,N*-dimethylformamide (5 mL). The reaction was stirred for 48 h and then diluted with ethyl acetate (100 mL). The solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 6:1 ethyl acetate/hexane gave 230 mg, (45%) of the desired product. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.49-7.56 (m, 3 H), 7.37-7.43 (m, 3 H), 7.17-7.23 (m, 2 H), 6.68-6.92 (m, 3 H), 4.09 (q, 3 H), 3.92-4.01 (m, 1 H), 3.75 (s, 3 H), 2.31-2.50 (m, 3 H), 1.62-1.77 (m, 1 H), 1.39 (s, 9 H), 0.98 (t, 3 H).

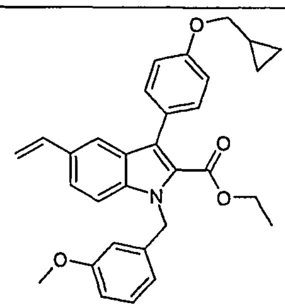
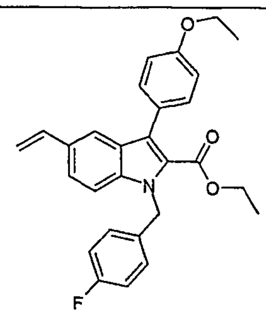
Example 129

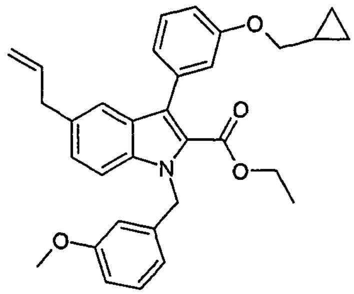
Ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-vinyl-1*H*-indole-2-carboxylate



Lithium chloride (297 mg, 7.0 mmol) and tributylvinyl tin (0.43 mL, 467 mg, 1.5 mmol) were added to a stirred solution of ethyl 3-(4-tert-butylphenyl)-1-(3-methoxybenzyl)-5-{[(trifluoromethyl)sulfonyl]oxy}-1H-indole-2-carboxylate (Example **125**, 570 mg, 0.995 mmol) in tetrahydrofuran (10 mL). Argon was bubbled through the mixture for 10 min and then tetrakis(triphenylphospine)palladium (115 mg, 0.10 mmol) was added. The reaction was heated (67 °C for 18 h and then cooled to rt. The mixture was diluted with ethyl acetate (100 mL) and then washed successively with water, 10% aqueous ammonium hydroxide, water and brine. The organic solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 10% ethyl acetate/hexane gave 334 mg (72%) of the desired product. The product had: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.58 (m, 8 H), 6.64-6.82 (m, 4 H), 5.77 (s, 2 H), 5.65 (dd, 1 H), 5.13 (dd, 1 H), 4.10 (q, 2 H), 3.73 (s, 3 H), 1.40 (s, 9 H), 0.95 (t, 3 H); mass spectroscopy gave MH^+ = 468.2 (calc'd exact mass for $C_{31}H_{33}NO_3$ = 467.25).

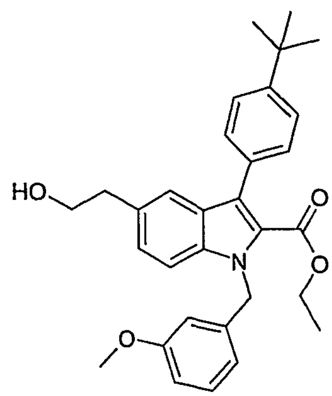
The following compounds were prepared according to the method of Examples **128 – 129:**

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
130		3	482.1	0.48 (Hexane/ethyl acetate 4:1)	
131		69		0.41 (Hexane/ethyl acetate 5:1)	

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
132		82	496.2		

Example 133

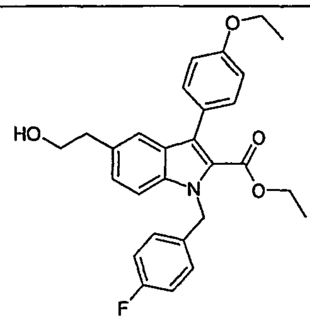
Ethyl 3-(4-*tert*-butylphenyl)-5-(2-hydroxyethyl)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate



Acetic acid (63 µL, 66 mg, 1.1 mmol) was added slowly to a cooled (0 °C) and stirred slurry of sodium borohydride (41.6 mg, 1.10 mmol) in tetrahydrofuran (2 mL). The mixture was stirred for 1 h and then a solution of ethyl 3-(4-tert-butylphenyl)-1-(3-methoxybenzyl)-5-vinyl-1*H*-indole-2-carboxylate (Example **129**, 430 mg, 0.920 mmol) in tetrahydrofuran (5 + 2 mL rinse) was added. The reaction was stirred overnight and then cooled (0 °C). The reaction was quenched by successive addition of EtOH (6 mL), 6 M aqueous sodium acetate (5 mL) and 27% aqueous hydrogen peroxide (5 mL). The mixture was heated (50 °C) for 1 h and then cooled. The reaction was diluted with water (100 mL) and then extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 30% ethyl acetate/hexane afforded 325 mg (75%) of desired product. The product had: ^{1}H

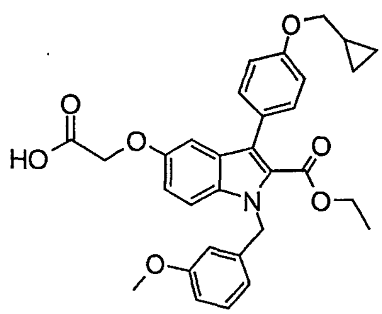
NMR (300 MHz, $CDCl_3$) δ 7.28-7.48 (m, 6 H), 7.15-7.22 (m, 2 H), 6.75 (dd, 1 H), 6.64-6.72 (m, 2 H), 7.76(s, 2 H), 4.08 (q, 2 H), 3.78-4.00 (m, 3 H), 3.73 (s, 3 H), 2.91 (t, 2 H), 1.39 (s, 9 H), 0.95 (t, 3 H).

The following compounds were prepared according to the method of Example **133**

Ex. No.	**Structure**	**Yield [%]**	**MS [M+H$^+$]**	**Rf**	**mp [°C]**
134		56	462.2		

Example 135

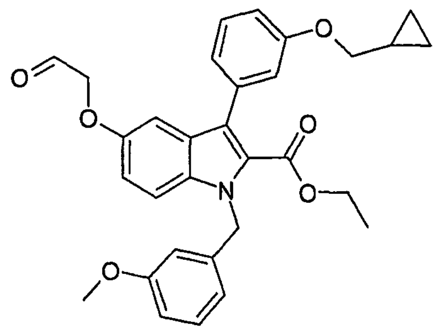
{[3-[4-(Cyclopropylmethoxy)phenyl]-2-(ethoxycarbonyl)-1-(3-methoxybenzyl)-1*H*-indol-5-yl]oxy}acetic acid



Formic acid (1 mL) was added to a stirred solution of ethyl 5-(2-*tert*-butoxy-2-oxoethoxy)-3-[4-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **150**, 20 mg, 0.035 mmol) in dichloromethane (1 mL). The reaction was stirred for 1 h and then concentrated *in vacuo*. Flash chromatography of the residue over silica gel using (1:1 ethyl acetate/hexane) gave 10 mg (53% of the desired product. The product had: ^{1}H NMR (300 MHz, CD_3OD) δ 7.30-7.48 (m, 3 H), 6.92-7.19 (m, 4 H), 6.77 (dd, 1 H), 6.54-6.68 (m, 3 H), 5.79 (s, 2 H), 4.61 (s, 2 H), 4.13 (q, 2 H), 3.95 (d, 2 H), 3.74 (s, 3 H), 1.29-1.41 (m, 1 H), 1.25 (t, 3 H), 0.61-0.71 (m, 2 H), 0.39-0.49 (m, 2 H); mass spectroscopy gave MH+ of 530.2 (calc'd exact mass for $C_{31}H_{31}NO_7$ = 529.21).

Example 136

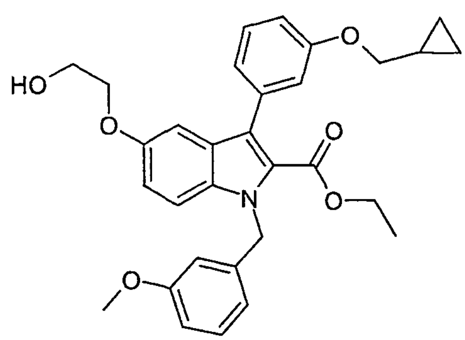
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-(2-oxoethoxy)-1*H*-indole-2-carboxylate



Sodium periodate (812 mg, 3.80 mmol) and osmium tetroxide (2.5 wt% solution in *tert*-butanol, 1.2 mL, 0.10 mmol) were added to a stirred solution of ethyl 3-[4-(cyclopropyl-methoxy)phenyl]-1-(3methoxy-benzyl)-5-allyloxy-1*H*-indole-2-carboxylate (Example **149**, 640 mg, 1.25 mmol) in tetrahydrofuran (15 mL) and water (1.5 mL). The reaction was stirred for 16 h and then diluted with water (100 mL). The product was extracted with ethyl acetate (3x50 mL) and then the combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 8:1 hexane/ethyl acetate gave 395 mg (62%) of product containing impurities. The material was used in the next reaction without further purification or analysis.

Example 137

Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-5-(2-hydroxyethoxy)-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate

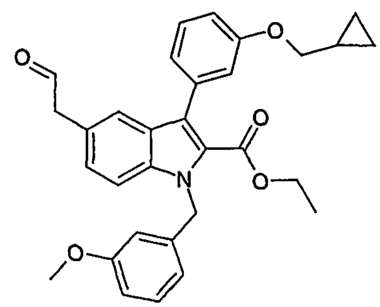


Sodium borohydride (38 mg, 1.0 mmol) was added to a stirred solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-(2-oxoethoxy)-1*H*-indole-2-carboxylate (Example **136**, 380 mg, 0.74 mmol) in methanol (10 mL). The reaction was

stirred for 2 h and then the reaction was quenched with water (100 mL). The product was extracted with ethyl acetate (3x40 mL) and then the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to leave 363 mg (95%) of product containing some impurities. The material was used in the next reaction without further purification. The product had: ^{1}H NMR (300 MHz, acetone-D_6) δ 7.34-7.46 (m, 3 H), 7.16 (dd, 1 H), 6.93-7.02 (m, 4 H), 6.65-6.81 (m, 3 H), 5.78 (s, 2 H), 3.82-4.23 (m, 9 H), 3.69 (s, 3 H), 1.24-1.34 (m, 1 H), 1.02 (t, 3 H), 0.60-0.70 (m, 2 H), 0.34-0.44 (m, 2 H).

Example 138

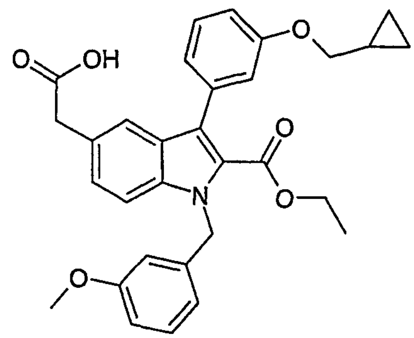
Ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl) -5-(2-oxoethyl)-1*H*-indole-2-carboxylate



Sodium periodate (430 mg, 2.0 mmol) and osmium tetroxide (2.5 wt% solution in *tert*-butanol, 0.50 mL, 0.05 mmol) were added to a stirred solution of ethyl 5-allyl-3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate (Example **132**, 385 mg, 0.777 mmol) in tetrahydrofuran (10 mL) and water (1 mL). The reaction was stirred for 18 h and then diluted with water (100 mL). The product was extracted with ethyl acetate (3x50 mL) and then the combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 15% ethyl acetate/hexane gave 183 mg (47%) of product containing impurities. The material was used in the next reaction without further purification. Mass spectroscopy gave MH^+ = 498.1 (exact mass calc'd for $C_{31}H_{31}NO_5$ = 497.22).

Example 139

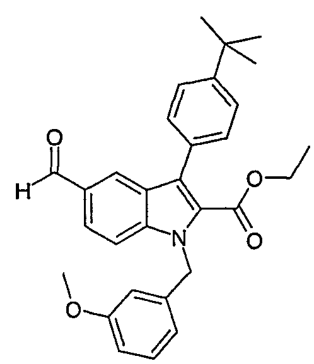
[3-[3-(Cyclopropylmethoxy)phenyl]-2-(ethoxycarbonyl)-1-(3-methoxybenzyl)-1H-indol-5-yl]acetic acid



2-Methyl-2-butene (2 mL), sodium phosphate monobasic (307 mg, 2.6 mmol) and sodium perchlorate (307 mg, 3.4 mmol) were added to a stirred solution of ethyl 3-[3-(cyclopropylmethoxy)phenyl]-1-(3-methoxybenzyl)-5-(2-oxoethyl)-1*H*-indole-2-carboxylate (Example **138**, 169 mg, 0.34 mmol) in *tert*-butanol (8 mL) and water (3 mL). The reaction was stirred for 24 h and then diluted with ethyl acetate (100 mL). The solution was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash chromatography of the residue over silica gel using 60% ethyl acetate/hexane afforded 35 mg (20%) of the product. The product had: ^1H NMR (300 MHz, acetone-D_6) δ 6.96-7.57 (m, 8 H), 6.58-6.80 (m, 3 H), 5.83 (s, 2 H), 4.11 (q, 2 H), 3.90 (d, 2 H), 3.70 (s, 3 H), 3.67 (s, 2 H), 1.24-1.40 (m, 1 H), 1.03 (t, 3 H), 0.55-0.65 (m, 2 H), 0.35-0.46 (m, 2 H); mass spectroscopy gave M-H^+ = 512.5 (calc'd exact mass for $C_{31}H_{31}NO_6$ = 513.22).

Example 140

Ethyl 3-(4-*tert*-butylphenyl)-5-formyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate

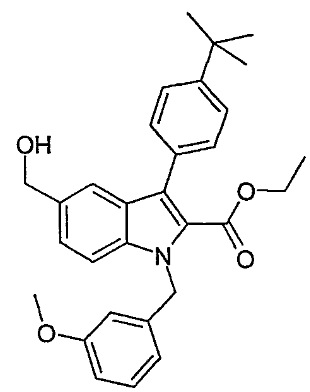


Ethyl 3-(4-*tert*-butylphenyl)-1-(3-methoxybenzyl)-5-vinyl-1H-indole-2-carboxylate (Example **129**, 2.28 g, 4.9 mmol) was dissolved in anhydrous tetrahydrofuran

(25 mL), and osmium tetroxide (2.5 weight % solution in 2-methyl-2-propanol, 1.5 mL, 0.15 mmol) was added. After ten minutes, the reaction mixture was cooled with an ice bath. Sodium periodate (2.10 g, 9.8 mmol) was added followed by a minimum volume of water to dissolve the solids. The reaction was allowed to return to room temperature, and after 30 minutes, the reaction was partitioned between water and diethyl ether. The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated. The resulting crude oil was passed through a pad of silica gel with 20% ethyl acetate/hexane. The filtrate was concentrated *in vacuo* without heat to provide the title compound as a brown oil (1.70g, 75%). The product had: ^{1}H NMR (300 MHz, acetone-d_6) 10.01 (s, 1 H), 8.15 (d, 1 H), 7.88 (d, 1 H), 7.75 (d, 1 H), 7.54 (d, 2 H), 7.44 (d, 2 H), 7.21-7.19 (m, 1 H), 6.81-6.79 (m, 1 H), 6.72-6.69 (m, 2 H), 5.92 (s, 2 H), 4.12 (q, 2 H), 3.71 (s, 3 H), 1.39 (s, 9 H), 0.78 (t, 3 H).

Example 141

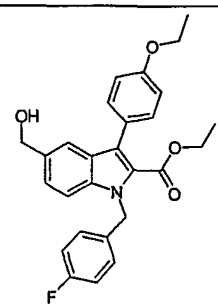
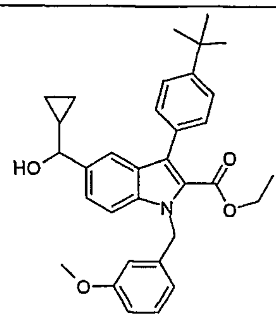
Ethyl 3-(4-*tert*-butylphenyl)-5-(hydroxymethyl)-1-(3-methoxybenzyl)-1H-indole-2-carboxylate



Ethyl 3-(4-*tert*-butylphenyl)-5-formyl-1-(3-methoxybenzyl)-1H-indole-2-carboxylate (Example **140**, 700 mg, 1.493 mmol) was dissolved in ethanol (15 mL) and cooled to 0 °C. Sodium borohydride (57 mg, 1.50 mmol) was added, and the solution was stirred for 1 hour. Water (27 µL, 1.5 mmol) was added, and the mixture was allowed to warm to room temperature. The mixture was concentrated via rotary evaporation, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The resulting crude oil was purified by flash chromatography on silica gel eluted with hexane then 20% ethyl acetate/hexane. The title compound was collected as a foam (530 mg, 75%). The product had: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.56-7.55 (m, 1 H), 7.53-7.51

(m, 1 H), 7.50-7.47 (m, 2 H), 7.41-7.39 (m, 1 H), 7.37-7.34 (m, 2 H), 7.18-7.16 (m, 1 H), 6.77-6.75 (m, 1 H), 6.68-6.70 (m, 2 H), 5.85 (s, 2 H), 4.65 (d, 2 H), 4.09 (q, 2 H), 4.06-4.04 (m, 1 H), 3.70 (s, 3 H), 1.38 (s, 9 H), 0.96 (t, 3 H); mass spectroscopy gave MH^+ = 472.2 (calc'd exact mass for $C_{30}H_{33}NO_4$ = 471.24).

The following compounds were prepared according to the method of Example **141**:

Ex. No.	Structure	Yield [%]	MS [M+H$^+$]	Rf	mp [°C]
142		97	448.1		
143		crude			

Example 144

Ethyl 3-[4-(cyclopropylmethoxy)phenyl]-5-ethoxy-1-(3-methoxybenzyl)-1*H*-indole-2-carboxylate